Simultaneous Population Optimal Design for Pharmacokinetic-Pharmacodynamic Experiments

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ABSTRACT

Multiple outputs or measurement types are commonly gathered in biological experiments. Often, these experiments are expensive (such as clinical drug trials) or require careful design to achieve the desired information content. Optimal experimental design protocols could help alleviate the cost and increase the accuracy of these experiments. In general, optimal design techniques ignore between-individual variability, but even work that incorporates it (population optimal design) has treated simultaneous multiple output experiments separately by computing the optimal design sequentially, first finding the optimal design for one output (eg, a pharmacokinetic [PK] measurement) and then determining the design for the second output (eg, a pharmacodynamic [PD] measurement). Theoretically, this procedure can lead to biased and imprecise results when the second model parameters are also included in the first model (as in PK-PD models). We present methods and tools for simultaneous population D-optimal experimental designs, which simultaneously compute the design of multiple output experiments, allowing for correlation between model parameters. We then apply these methods to simulated PK-PD experiments. We compare the new simultaneous designs to sequential designs that first compute the PK design, fix the PK parameters, and then compute the PD design in an experiment. We find that both population designs yield similar results in designs for low sample number experiments, with simultaneous designs being possibly superior in situations in which the number of samples is unevenly distributed between outputs. Simultaneous population D-optimality is a potentially useful tool in the emerging field of experimental design.

KEYWORDS: pharmacokinetics, pharmacodynamics, D-optimality, estimator, bias, precision, experiment design

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INTRODUCTION

Pharmacokinetic and pharmacodynamic (PK-PD) modeling techniques have become an indispensable tool in drug development. PK-PD modeling is used both to determine how a drug is absorbed, distributed, metabolized, and excreted in an animal or human (PK modeling) and to identify the primary in vivo properties of a drug such that the magnitude and time course of the *response* to that drug can be predicted under normal and pathological conditions (PD modeling).[1,2] Over the past decade, PK-PD modeling has gone from a mostly empirical pursuit to a mechanistically based predictive discipline that has been employed in nearly all aspects of drug development.[3] The Food and Drug Administration (FDA) has recognized this development and in 1997 and 1998 released guidelines that strongly encourage the use of PK-PD information to facilitate the approval of new drugs based on fewer clinical trials and more advanced analysis of those trials.[4,5]

However, if we are to use fewer clinical trials to approve drugs, the quality of these trials must improve. The present methods of designing clinical trials often result in experiments that have unreliable or inaccurate results,[6] requiring the trials to be rerun and increasing costs and time for development. Recent studies have found that research and development costs associated with FDA approval of a drug are between $500 million and $802 million and development time is roughly 10 to 12 years.[7,8] As a result, the field of optimal experimental design has emerged to try and understand the important aspects of clinical trial design, and to then optimize those influential factors. One of the many influential aspects of clinical trial design is effective sampling. That is, determining when samples are collected, how many samples are collected, and, in the case of population models, from how many individuals the samples are collected. Studies have demonstrated that the accuracy of mixed-effect model (the type of models used in PK-PD experiments) parameter estimates is highly dependent on these sampling questions,[6,9] and it is this aspect of clinical trial design that we explore in this study.

Most methods of optimal design are based on the Fisher information matrix (FIM), which provides an asymptotic

Table 1. Design Protocols for Model 1, A Mono-exponential PK, No Effect Site and Emax PD Model*

Protocol	Number of PK Samples per Individual (n_{pk})	Number of PD Samples per Individual (n_{pd})	Design Type
n_{pk}-n_{pd}-Sim	1-2	1-3	Simultaneous population D-optimal
n_{pk}-n_{pd}-Seq	1-2	1-3	Sequential population D-optimal
2-3-Std	2	3	Sequential standard D-optimal ($\vec{b}_i = 0$)

*PK indicates pharmacokinetic and PD, pharmacodynamic.

lower bound on the covariance matrix of the estimated model parameters.[10] In the most common of these approaches, so-called D-optimal design, the determinant of the inverse of the FIM is minimized based on the variables of an experimental design.[11] One of the main problems with optimal design of population experiments is that the FIM is often very difficult and time consuming to calculate. As a result, various simplifications are made to the FIM. The most popular simplification has been to design population studies by developing a D-optimal design for an individual study (ie, no between-subject variability is considered in the design), and then applying that design to each individual in a population study (where between-subject variability is present).[12] This standard D-optimal design approach is computationally tractable; however, because it does not take into account between-subject variability, its designs can be, in some sense, suboptimal, particularly if knowledge of between-subject variability is important (eg, to determine likely ranges of drug safety and toxicity in a population).[13]

More recent studies have investigated D-optimal design strategies that incorporate between-subject variability into the experimental design and focus on estimating population distributions of parameters rather than individual values.[14-17] These population D-optimal design strategies are algorithmically more intensive than standard D-optimal design strategies and require additional information for computation (between-subject variability information).

However, in all of these studies the approach has been to compute designs for single output experiments. As such, all multiple output experimental design calculations (such as in PK-PD experiments) have been approximated by a set of either individual or population sequential single output experiments.[18] These single-output designs are then merged into a multiple output PK-PD experimental design. This approach could be considered the optimal design equivalent of a sequential population PD-PD analysis. As with sequential analysis, there are 2 main theoretical problems with sequential optimal design. First, because of the hierarchical nature of the PK-PD models, some PK parameters are found in the PD models. In sequential analysis, by fixing the PK parameters before estimating the PD parameters, the PD parameter estimates and standard errors may be unrealistically good (because the error of the PK parameters is not properly accounted for) and the PK parameters unrealistically bad (because the PD data contain information about the PK model).[19] In sequential

Table 2. Design Protocols for Model 2: A Mono-exponential PK Linked to an Emax PD Model via a First-order Effect Site*

Protocol	Number of PK Samples per Individual (n_{pk})	Number of PD Samples per Individual (n_{pd})	Design Type
n_{pk}-n_{pd}-Sim	1-2	1-6	Simultaneous population D-optimal
n_{pk}-n_{pd}-Seq	1-2	1-6	Sequential population D-optimal
2-6-Std	2	4-6	Sequential standard D-optimal ($\vec{b}_i = 0$)

*PK indicates pharmacokinetic and PD, pharmacodynamic.

Table 3. Design Protocols for Model 3: A 2-compartment PK Model With No Effect Site and an Emax PD Model*

Protocol	Number of PK Samples per Individual (n_{pk})	Number of Samplesper Individual (n_{pd})	PD Design Type
n_{pk}-n_{pd}-Sim	1-4	1-3	Simultaneous population D-optimal
n_{pk}-n_{pd}-Seq	1-4	1-3	Sequential population D-optimal
4-3-Std	4	3	Sequential standard D-optimal ($\vec{b}I = 0$)

*PK indicates pharmacokinetic and PD, pharmacodynamic.

optimal design, the same problem occurs; by fixing the PK parameters, the optimized PD designs will not allow for optimal PK parameter estimation, while the PK designs will not assume information can come from the PD measurements. The second theoretical problem with sequential optimal design is that, by separating each type of measurement and then calculating separate designs, estimate correlations between the model parameters describing different measurement types are not incorporated into the optimality measure.

At present, simultaneous population PK-PD modeling is routinely being used (for example, see Danhof et al[20]). Just as sequential analysis is an approximation to the "gold standard" of sequential analysis,[19] sequential optimal design is an approximation to the "gold standard" of simultaneous optimal design. In addition, it seems to make theoretical sense to optimize an experiment in the same manner that it is analyzed. As such, we would like to explore and compare the effects of using simultaneous and sequential optimal design techniques in various situations.

In this study, we present a novel way of looking at optimal design by creating a design strategy based on multiple measurement population PK-PD models. Specifically, we investigate *simultaneous* population D-optimal designs of PK-PD experiments. To do this, we use 4 multiple-measurement PK-PD models to compare our novel simultaneous population D-optimal designs (SIM) with both population (SEQ) and standard (STD) sequential D-optimal designs (non-population-based). We evaluate these various design strategies through examination of the asymptotically predicted variances in the FIMs and through simulation/estimation experiments.

BACKGROUND

The main concepts of population modeling and optimal design theory have been widely discussed.[16,21-23] In this study, we follow the same notation as in our previous work,[24] the implementation of which has been elucidated in Foracchia et al.[25] However, in this work we are considering PK-PD experiments, which entail more complexity than single output experiments. We focus on this added complexity in this section.

Population Models

For a specific measurement type in the system (ie, the PK and PD measurements) we denote as $\vec{y}_i$ the vector of n measurements for individual

$$\vec{y}_i = f(\vec{x}_i, \vec{\beta}_i) + \vec{\varepsilon}_i, \quad \vec{\varepsilon}_i \sim N(0, \mathbf{R}_i(\vec{x}_i, \vec{\beta}_i)), \qquad (1)$$

Table 4. Design Protocols for Model 4: for the Oral Dosing of Theophylline*

Protocol	Number of PK Samples per Individual (n_{pk})	Number of PD Samples per Individual (n_{pd})	Design Type
n_{pk}-n_{pd}-Sim	1-3	1-6	Simultaneous population D-optimal
n_{pk}-n_{pd}-Seq	1-3	1-6	Sequential population D-optimal
3-6-Std	3	6	Sequential standard D-optimal ($\vec{b}i = 0$)

*PK indicates pharmacokinetic and PD, pharmacodynamic.

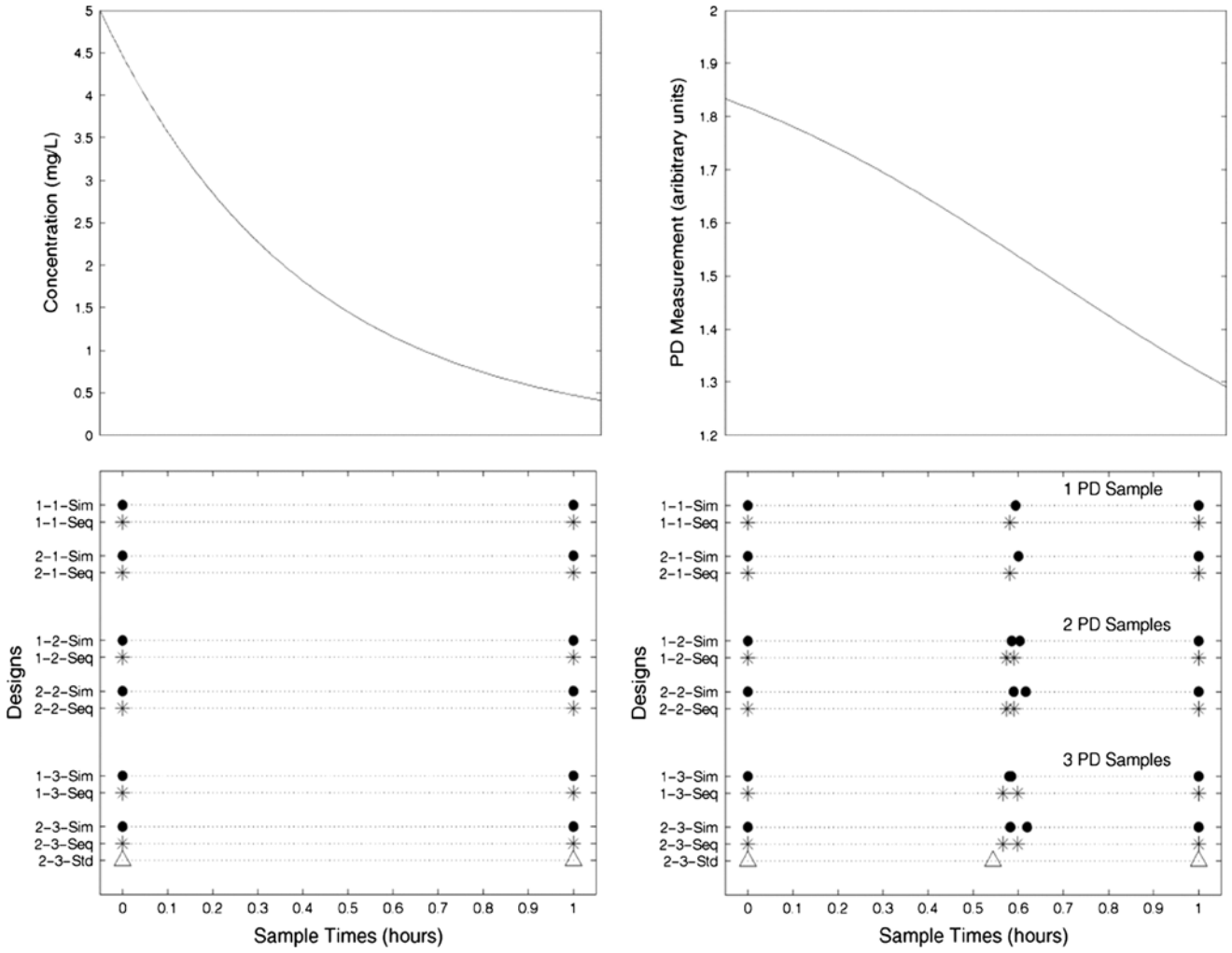

Figure 1. Sampling times for each design considered in Model 1. For each design, all sample times from all individuals are plotted together on one line. The left figure shows the PK sample times and the right figure shows the PD sample times. (Δ)- STD SEQ optimal times, (*)- SEQ population optimal times, (•)- SIM population optimal times. The population model mean PK and PD response curves are shown above their respective sampling times. The designs are shown to be similar for all design methods.

where $\vec{\epsilon}_i$ is the measurement error, $f(\vec{x}_i, \vec{\beta}_i)$ is a generic model, $\vec{x}_i$ are the experimental variables (eg, sample times), and $\vec{\beta}_i$ are the parameters (eg, rate constants and volumes of distribution) of the model. We assume that $\mathbf{R}_i(\vec{x}_i, \vec{\beta}_i)$ is diagonal but not necessarily homoscedastic and, as usual, we assume that the model parameters comprise fixed effects ($\vec{\beta}_{\text{pop}}$), random effects ($\vec{b}_i$), and covariates $\vec{a}_i$

$$\vec{\beta}_i = g(\vec{\beta}_{\text{pop}}, \vec{b}_i, \vec{a}_i), \quad \vec{b}_i \sim N(0, \mathbf{D}). \tag{2}$$

In addition, we assume the variance of the random effects, **D**, form a diagonal matrix and thus all random effects are independent from one another and from the variance of the measurement error, **R***i*.

Optimal Design Theory

The Cramer-Rao inequality[26] tells us that the covariance of a models' fitted parameters is greater than, and asymptotically approaches, the inverse of the FIM

$$Cov\hat{\vec{\theta}} \geq (\mathbf{FIM})^{-1}. \tag{3}$$

The FIM is defined as

$$\mathbf{FIM} = E_{\vec{y}}\left[\left(\frac{\partial}{\partial\vec{\theta}}L(\vec{\theta})\right)^T \frac{\partial}{\partial\vec{\theta}}L(\vec{\theta})\right] \tag{4}$$

where $E_{\vec{y}}[\,]$ indicates the expectation with respect to all the data in the population experiment $\vec{y}$ and $L(\vec{\theta})$ is the log-likelihood of the observations given the population parameters $\vec{\theta}$. This then gives us a way to compute our optimal designs; by minimizing the inverse of the FIM we minimize the asymptotic lower bound for our estimated model parameters.

Practically, the minimization of the inverse of the FIM is done by reducing the matrix to a scalar in some manner and then extremizing that scalar quantity. In this work we use the most common scalarization called D-optimality (which we denote as JD). In D-optimality we fix $\vec{\theta}$ to our best estimate of the model parameters, $\vec{\theta}$ Best.

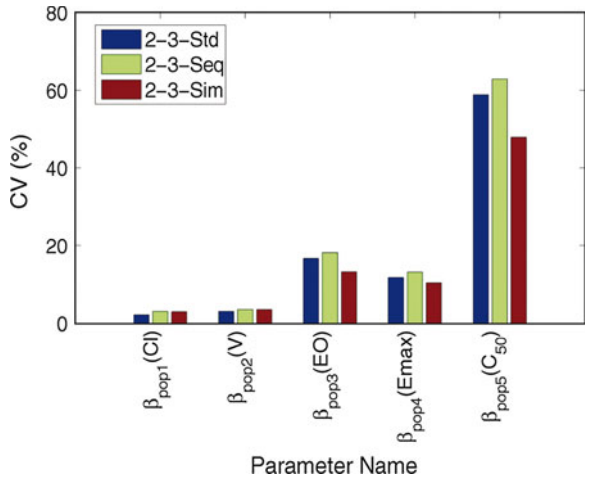

Figure 2. CVs for the SIM, SEQ, and STD 2_{pk} - 3_{pd} designs considered in Model 1. Differences are evident for the 3 fixed effects of the PD model.

Then, we minimize the determinant of the inverse of the FIM with respect to the design parameters, or, equivalently, maximize the determinant of the FIM,[16]

$$Max_{\vec{x}}[J_D] = Max_{\vec{x}}\left[Det\left(\mathbf{FIM}\left(\vec{x}, \vec{\theta}_{\text{Best}}\right)\right)\right]. \qquad (5)$$

One drawback of this optimization method is that all model parameters are considered equally important to estimate accurately. It is easy to imagine scenarios where one parameter may be more important than another to estimate accurately. The FIM could be optimized in such situations using, for example, the DS-optimality criterion used in other contexts (eg, in Solkner).[27] This criterion has been mentioned recently in the context of PK-PD experiments.[28]

Computation of the Population Fisher Information Matrix

The key to optimal design is the computation and optimization of the FIM. To compute the FIM we use Equation 2. However, because most of the models used in these computations are nonlinear with respect to their parameters, an analytical expression for the log-likelihood is not feasible. However, by linearizing the model about the expectation of the random effects parameters $\vec{b}_{j,i} = 0$, we can compute the log-likelihood of the model and thus derive an expression for the population **FIM** based on the individual $\mathbf{FIM}_i$[25]:

$$\begin{aligned}\mathbf{FIM}(\vec{\theta}) &= \sum_{i=1}^{m} \mathbf{FIM}_i(\vec{\theta}) \\ &= \sum_{i=1}^{m} \begin{bmatrix} \mathbf{M}_{1i} & 0 \\ \mathbf{M}_{2i} & \mathbf{M}_{3i} \end{bmatrix}^T \begin{bmatrix} Var(\vec{y}_i)^{-1} & 0 \\ 0 & \mathbf{M}_{4i}^{-1} \end{bmatrix} \\ &\quad \times \begin{bmatrix} \mathbf{M}_{1i} & 0 \\ \mathbf{M}_{2i} & \mathbf{M}_{3i} \end{bmatrix}\end{aligned} \qquad (6)$$

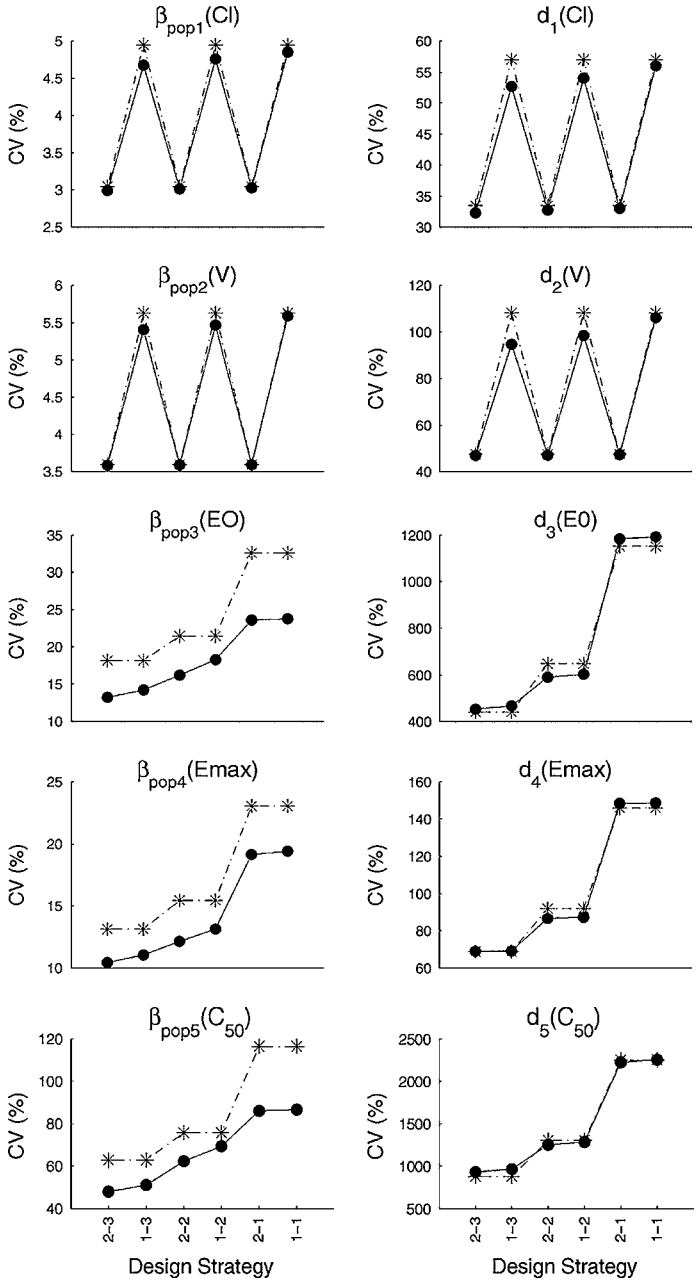

Figure 3. CVs for the SIM and SEQ population designs considered in Model 1. Differences are clear for the 3 fixed effects of the PD model. (*)- SEQ population optimal designs, (•)- SIM population optimal designs.

where

$$\begin{aligned}\mathbf{M}_{1i} &= \frac{\partial f(\vec{x}_i, \vec{\beta}_{pop})}{\partial \vec{\beta}_{pop}} \\ \mathbf{M}_{2i} &= \frac{\partial vec(Var(\vec{y}_i))}{\partial \vec{\beta}_{pop}} \\ \mathbf{M}_{3i} &= \frac{\partial vec(Var(\vec{y}_i))}{\partial \vec{d}} \\ \mathbf{M}_{4i} &= 2Var(\vec{y}_i) \otimes Var(\vec{y}_i)\end{aligned} \qquad (7)$$

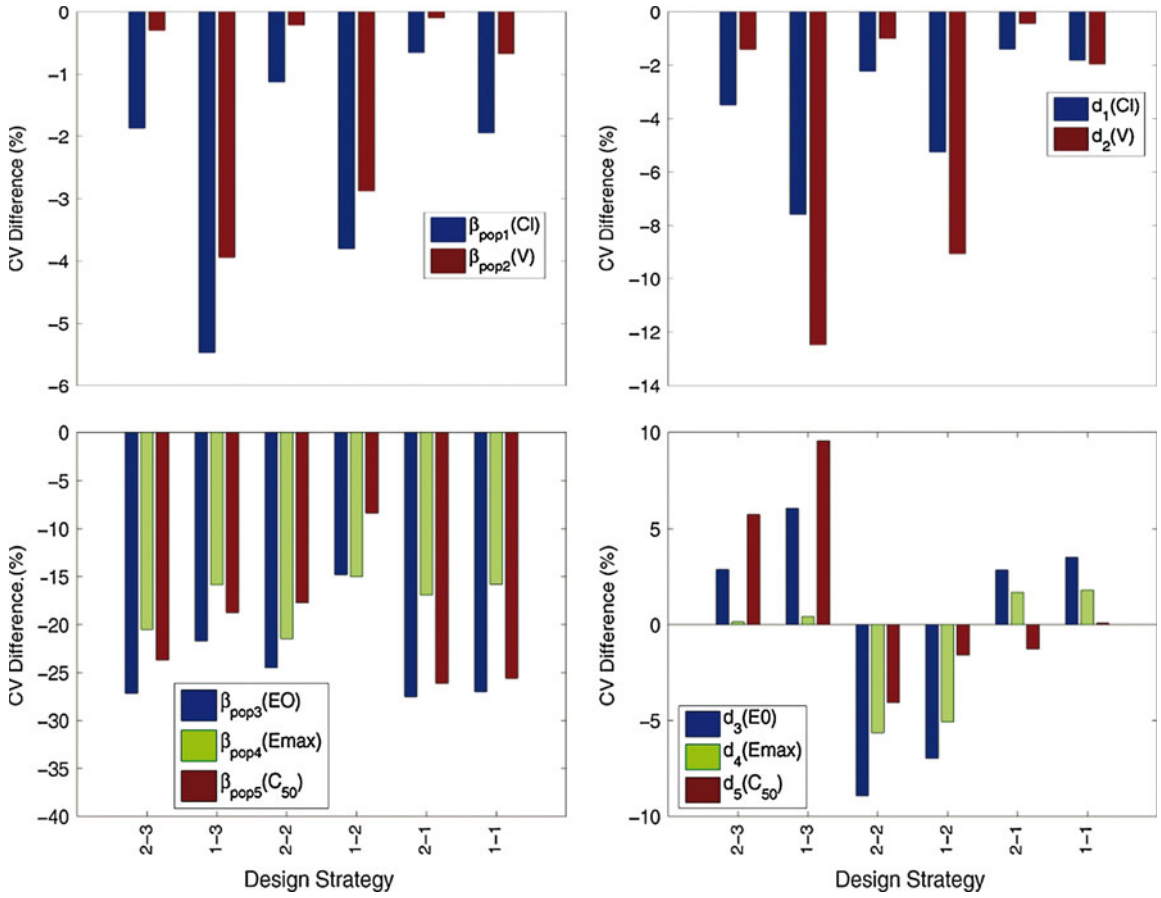

Figure 4. The percentage difference between the CVs predicted by the SIM and SEQ population optimal designs of Model 1, calculated as $(CV_{sim} - CV_{seq})/CV_{seq}$. A negative value means the SIM design predicts a smaller CV. The top 2 plots show the PK parameter CV differences; the bottom 2 plots show the PD parameter CV differences.

and the operator $vec()$ row vectorizes the matrix and $Var(\vec{y}_i)$ indicates the variance of the linearized model.

Grouping of Individuals in Population FIM Calculations

Regrettably, the computation of the population FIM becomes burdensome rather quickly (especially during optimization, when numerous population FIM calculations are needed). We can mitigate this problem by grouping individuals with similar characteristics and assuming that they will all have the same experimental designs.[17] That is

$$\mathbf{FIM}\left(\vec{x},\vec{\theta}\right) = \sum_{i=1}^{m} \mathbf{FIM}_i\left(\vec{x}_i,\vec{\theta}_i\right) = \sum_{i=1}^{N_g} g_i \mathbf{FIM}_i\left(\vec{x}_i,\vec{\theta}_i\right), \quad (8)$$

where N_g is the number of groups that make up the population, g_i are the number of individuals in group i, and

$$m = \sum_{i=1}^{N_g} g_i.$$

This grouping procedure not only reduces the size of the population FIM calculation but it also simplifies the optimization of the FIM. For example, if we are optimizing over sample times, the number of optimization variables, N_{vars}, is $\Sigma_{i=1}^{m} n_i$.

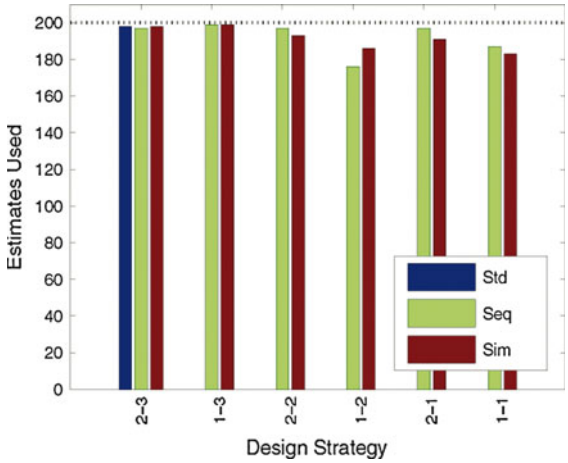

Figure 5. The number of simulation/estimation studies used to compare the various designs for Model 1. Two hundred simulations were attempted for all designs, but some parameter estimates were subsequently thrown out owing to numerical issues.

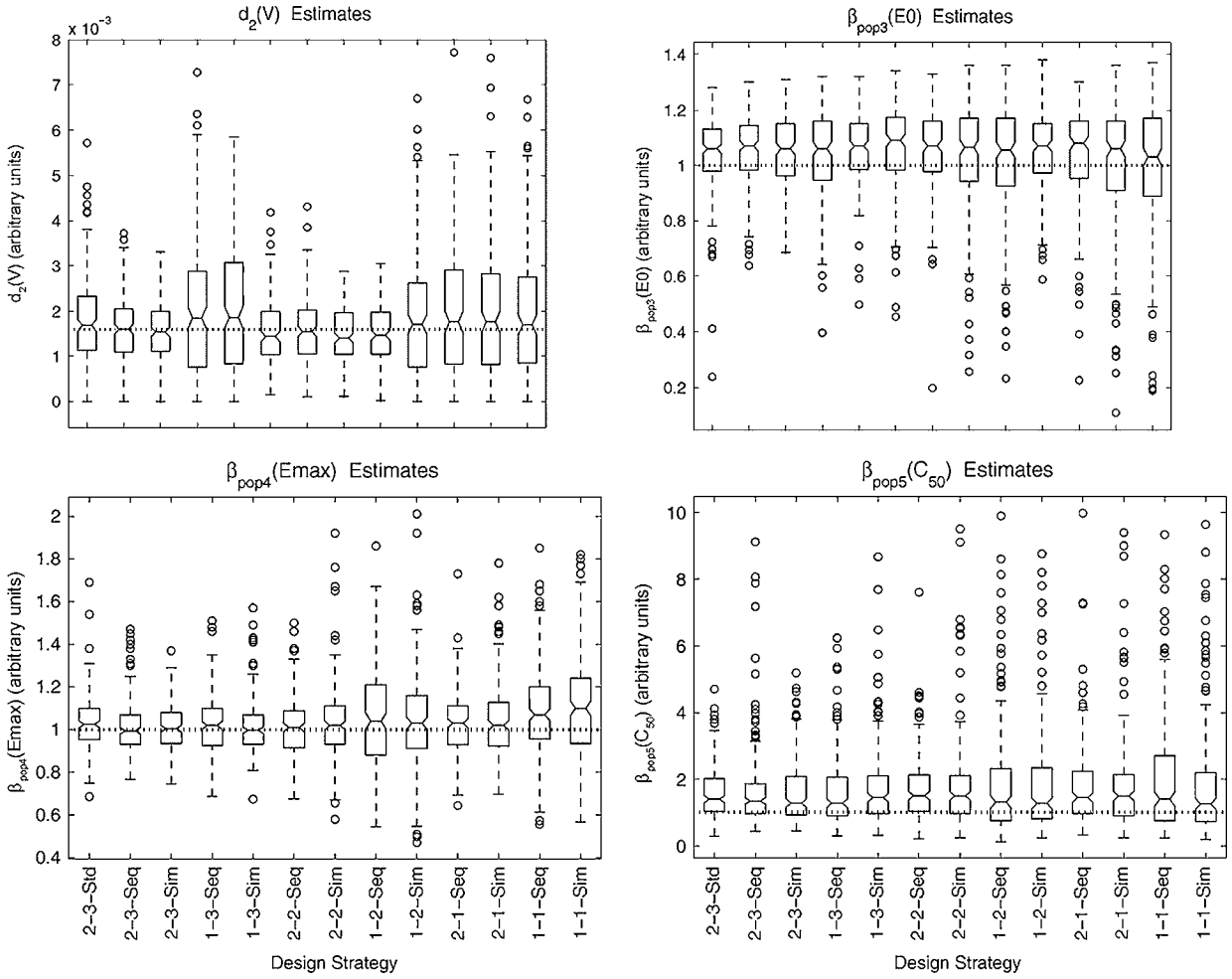

Figure 6. Box plots of parameter estimates for Model 1 using the design strategies outlined in Table 1. The dotted horizontal line is the true parameter value used in the simulations.

However, using the grouping procedure, $N_{vars} = \Sigma_{i=1}^{N_g} n_{g,i}$, a savings of $\Sigma_{i=1}^{N_g}(g_i - 1)n_{g,i}$ design points. This benefit can be significant if the number of individuals in an experiment is large. Of course, this simplification does reduce our ability to find the global optimum to this problem, but the benefits in speed may outweigh the disadvantages.

We reported a specific example of the effects of this grouping procedure on the trial design results.[25] In this study, we compare a full design with a grouped design, where N_g was 75% less than m. We found the grouping solution to be a good approximation to the total solution, with the determinant of the FIM decreased by only 8% and the design points at nearly the same locations.

Sequential and Simultaneous Model Fitting

In general, there are 2 basic methods employed to the fitting of PK-PD (or multiple-output) models: sequential (SEQ) fitting and simultaneous (SIM) fitting. In SEQ fitting, the parameters used to describe one output are estimated first. These parameters are then fixed and assumed known in the fitting of the other outputs.

The following is an example of a PK-PD experiment with 2 basic measurements. A set of data from the PK measurement vector, $\vec{y}_1,i$, is fit to an appropriate model

$$\vec{y}_{1,i} = f_1\left(\vec{x}_{1,i}, \vec{\beta}_{1,i}\right) + \vec{\varepsilon}_{1,i},$$
$$\vec{\varepsilon}_{1,i} \sim N\left(0, \mathbf{R}_{1,i}\left(\vec{x}_{1,i}, \vec{\beta}_{1,i}\right)\right). \quad (9)$$

The fitted parameters of this model, $\hat{\vec{\beta}}_1,i$, are then fixed to their fitted values and these values are used in the model that describes the set of data from the PD measurement vector,

$$\vec{y}_{2,i} = f_2\left(\vec{x}_{2,i}, \hat{\vec{\beta}}_{1,i}, \vec{\beta}_{2,i},\right) + \vec{\varepsilon}_{2,i},$$
$$\vec{\varepsilon}_{2,i} \sim N\left(0, \mathbf{R}_{2,i}\left(\vec{x}_{2,i}, \hat{\vec{\beta}}_{1,i}, \vec{\beta}_{2,i}\right)\right). \quad (10)$$

By replacing actual parameter values with independently fitted, fixed parameter values, SEQ modeling attempts to mitigate the potential for attenuation bias in the estimation of the second measurement-type model parameters.[21] However, this fitting method will often result in an unrealistically good estimate of the PD set of parameters, $\hat{\vec{\beta}}_{2,i}$, owing

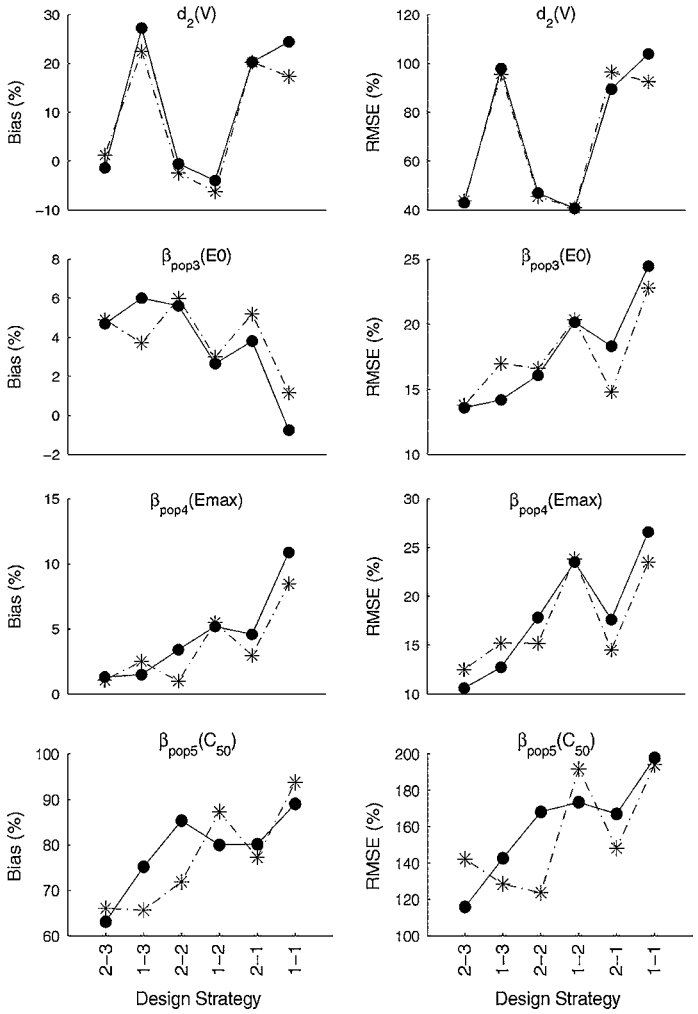

Figure 7. The percentage bias and RMSE for parameters in Model 1. Design methods are outlined in Table 1. (*)- SEQ population optimal designs, (•)- SIM population optimal designs.

to the fixed parameters and the resulting built-in lack of estimate correlation between the 2 sets of parameters.

In SIM modeling, the idea is to fit all measurements at the same time to avoid biased secondary parameters. One method of SIM modeling assumes that there is no correlation between the parameters associated with the different measurement vectors. This assumption allows us to easily write the probability density of the individual model output for all measurements $\vec{y}_i$ as a product of the probability densities for each different measurement vector $\vec{y}_{j,i}$

$$p\left(\vec{y}_i|\vec{\theta}\right) = \prod_{j=1}^{mt} p\left(\vec{y}_{j,i}|\vec{\theta}_j\right), \qquad (11)$$

where *mt* is the number of measurement vectors in the experiment and $\vec{\theta}_j$ are each model's population parameters.[29]

A more complete (and more complex) method of SIM modeling is to assume that all parameters $\vec{\theta}_j$ associated with all measurement vectors $\vec{y}_{j,i}$ are correlated in some way. To do this the probability density of the model is written as[30]

$$p\left(\vec{y}_i|\vec{\theta}\right) = p\left(\vec{y}_{1,i}\cdots\vec{y}_{mt,i}|\vec{\theta}_1,\cdots,\vec{\theta}_{mt}\right). \qquad (12)$$

When we use this method of SIM fitting, we get a full covariance matrix covering all the parameters.

Multiple Measurement Population FIM Calculations

In optimal design, the computation of the population FIM for PK-PD experiments (experiments with multiple types of measurements) can also be approached either simultaneously or sequentially. All previous work has used SEQ optimal design techniques in which the optimal design of the PK model is computed separately from the optimal design for the PD model. In this approach, any PK model parameters that appear in the PD model ($\vec{\beta}_{1,i}$ in Equations 9 and 10) are assumed known. That is, the experiment is not designed to estimate those parameters. Again, the problem with this approach is that there is a built-in lack of correlation between the PK and PD parameters in the design calculations.

In SIM optimal design of PK-PD experiments, we use a full FIM with correlations between PK and PD parameters in our design calculations. These methods are similar to those presented by Draper and Hunter[31] for multiresponse situations. These computations are more complex than for experiments with one measurement vector, but the theory does not change. That is, we can still use Equations 6 and 7; our model is just a bit more complicated. For each individual we have *mt* different types of measurements in our experiment

$$\vec{y}_i = \left[\left(\vec{y}_{1,i}\right)^T, \left(\vec{y}_{2,i}\right)^T, \cdots, \left(\vec{y}_{mt,i}\right)^T\right]. \qquad (13)$$

Each of these *mt* measurement types is associated with a different model, $f_1, f_2, \ldots, f_{mt}$, which we can group together to form a multiple measurement vector model

$$f\left(\vec{x}_i, \vec{\beta}_i\right) = \begin{cases} f_1\left(\vec{x}_{1,i}, \vec{\beta}_{1,i}\right) \\ f_2\left(\vec{x}_{2,i}, \vec{\beta}_{2,i}\right) \\ \vdots \\ f_{mt}\left(\vec{x}_{mt,i}, \vec{\beta}_{mt,i}\right) \end{cases} \qquad (14)$$

where $\vec{x}_i = \left[\left(\vec{x}_{1,i}\right)^T, \cdots, \left(\vec{x}_{mt,i}\right)^T\right]$ and $\vec{\beta}_i$ contains all parameters from all the measurement models (the same parameter appearing in 2 different models appears only once in $\vec{\beta}_i$.

This multiple measurement PK-PD model can now be described by the typical population model equations (Equations 1 and 2). We note that $\mathbf{R}_i$ in Equation 1 now includes

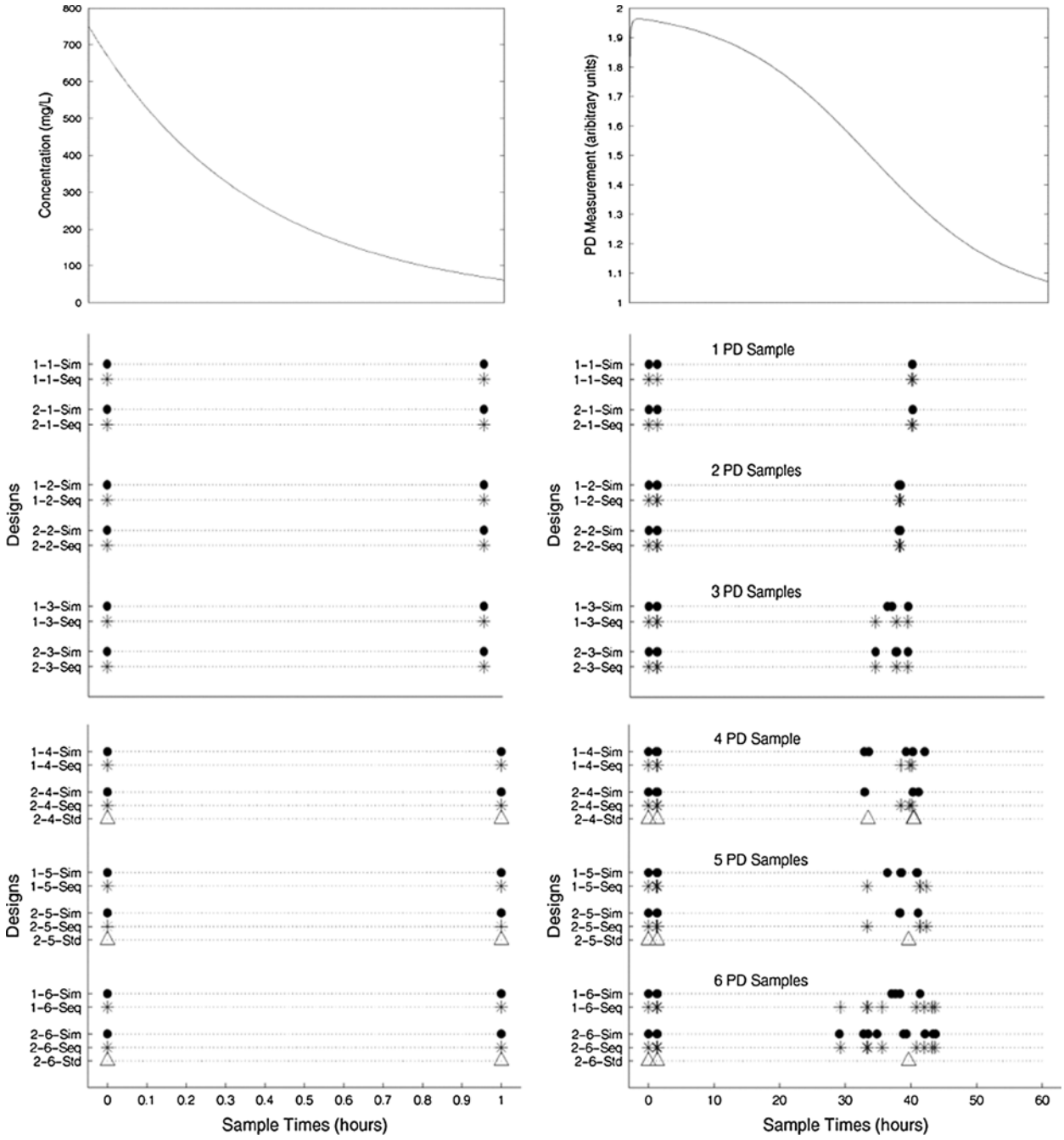

Figure 8. Sampling times for each design considered in Model 2. For each design, all sample times from all individuals are plotted together on one line. The left figure shows the PK sample times and the right figure shows the PD sample times. (Δ)- SEQ STD optimal times, (*)- SEQ population optimal times, (•)- SIM population optimal times. The population model mean PK and PD response curves are shown above their respective sampling times.

the measurement variances r_i from both PK and PD measurements in the experiment $\vec{y}_i$. The vectors $\vec{\beta}_{pop}$, $\vec{b}_i$, and $\vec{a}_i$, in Equation 2 contain all values from both the PK and PD measurement models, with values repeated in both models included only once in these vectors. Finally, **D** in Equation 2 now contains all random effect variances d_i from both measurement models (again if a parameter is included in 2 or more models it is included only once in **D**). Using these expanded definitions we can now use Equations 6 and 7 to calculate the SIM population FIM for PK-PD experiments.

METHODS

We begin this work by selecting 4 PK-PD models to use in our examination of sequential and simultaneous D-optimal designs. We assume that these models correctly describe the underlying PK-PD process and that the values for the model parameters are the "true" values of the

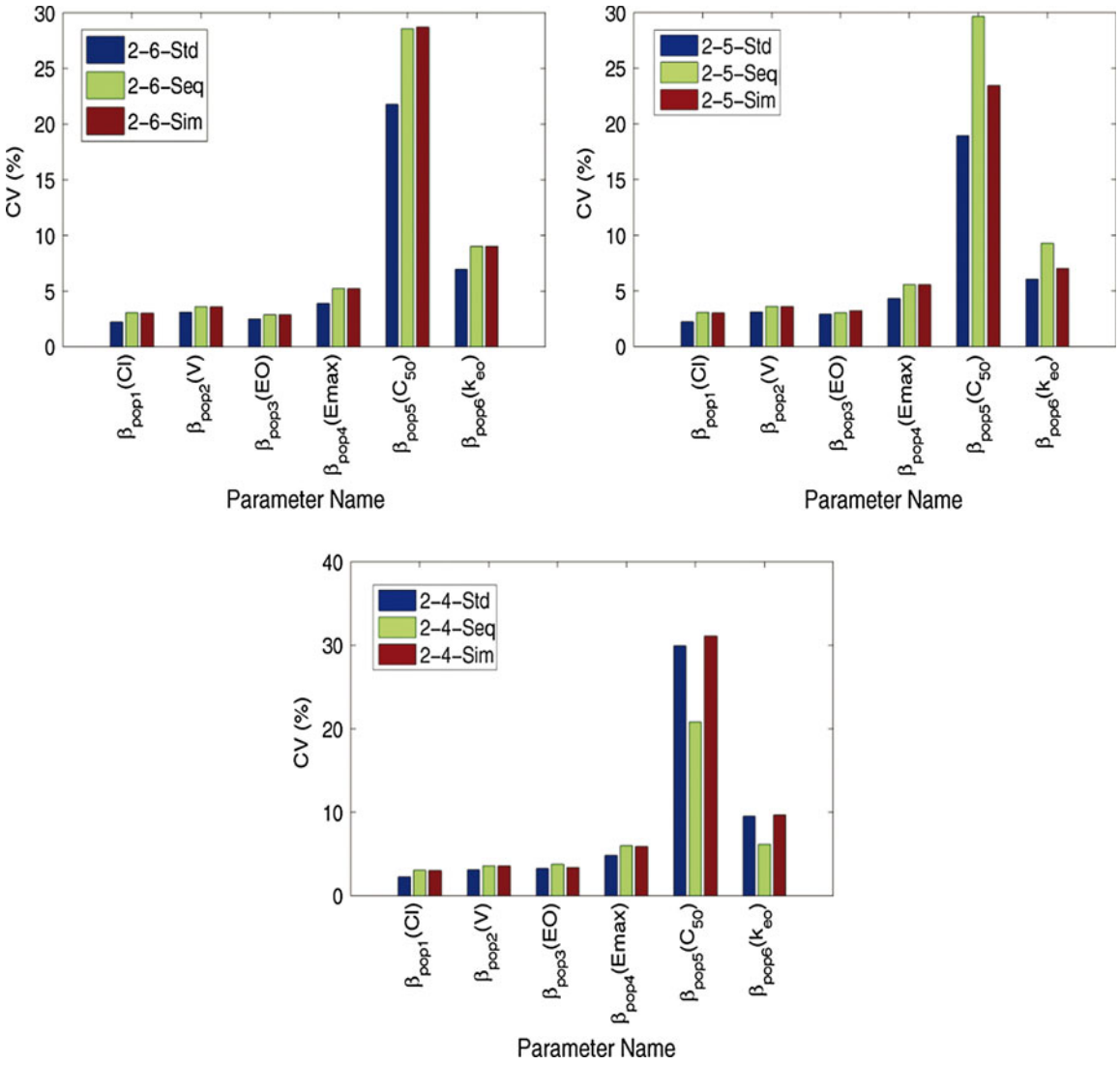

Figure 9. Model 2 CVs for designs in which all 3 design methods (SIM, SEQ, and STD) are used. Differences are clear for the β_{pop5} and β_{pop6} parameters.

parameters. Then, for each model, we calculate sequential non-population-based "standard" (STD) D-optimal designs, sequential (SEQ) population D-optimal designs, and simultaneous (SIM) population D-optimal designs. To compute the STD and SEQ D-optimal designs we use the software program PopED[25] (freely available from www.rfpk.washington.edu), which is written in the matrix-based computing environment O-Matrix (Harmonic Software, Seattle, WA). To compute the novel SIM D-optimal designs we modified the data structure in PopED to incorporate multiple models in the design calculations as described in the section entitled "Multiple Measurement Population FIM Calculations."

To compare these various designs, we first examine the resultant asymptotic parameter coefficients of variation (CVs) that the optimal FIMs provide looking for differences between the various design techniques. We also compute the percentage difference between the parameter CVs predicted by the SIM and the SEQ population design techniques as used by Retout and Mentré[28]

$$\text{CV Difference} = \frac{CV_{sim} - CV_{seq}}{CV_{seq}} \times 100\,\%. \qquad (15)$$

These percentage differences used in conjunction with the actual CV values can be used to better understand the differences between designs.

If differences between the various designs are found, we investigate them further through the type of simulation studies performed in Hooker et al.[24] Briefly, we simulate, using the software package NONMEM (Globomax, Hanover, MD), 200 replicate population PK data sets based on the D-optimal designs we calculated. That is, we use the same number of individuals, the same model parameter values, the same dosing strategy, etc, used to determine the optimal design and simulate data at the sampling times dictated by the optimal design calculations.

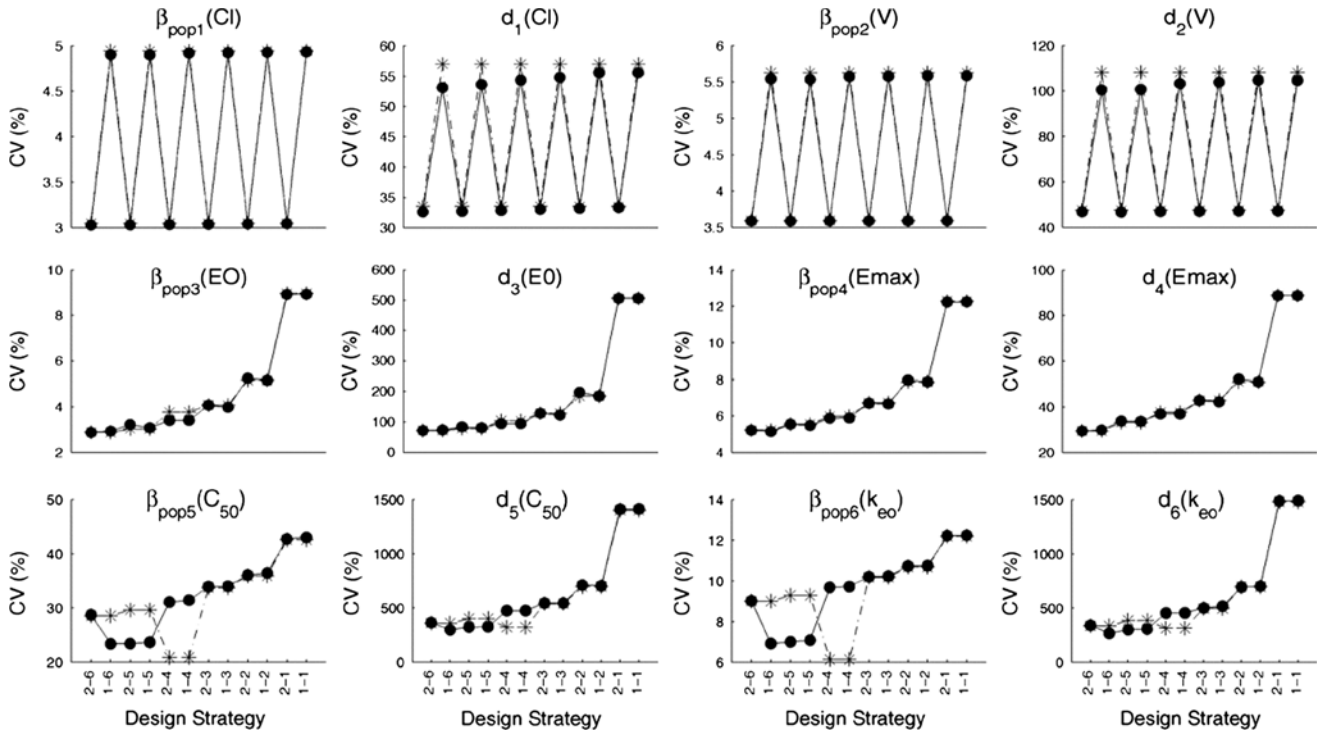

Figure 10. CVs for the SIM and SEQ population designs considered in Model 2. Differences are seen for d_1, d_2, β_{pop5}, and β_{pop6}. (*)- SEQ population optimal designs, (•)- SIM population optimal designs.

From this simulated data we then estimate (using the "first-order approximation" [FO] method in NONMEM) simultaneously the population PK-PD model parameters for each design and use these parameter estimates to compare the various designs. If NONMEM fails to converge, the estimates for that run are thrown out; the number of runs thrown out for each model is reported in our results. We compare the replicate estimated parameter values between designs by looking at box plots of the parameter estimates of each design, and then looking at the bias and root mean standard error (RMSE) of the parameter estimates. The bias can be used as a measure of the central tendency of the distribution of parameter estimates and is defined as follows[32]:

$$\frac{1}{\theta_k^{(TRUE)}}\left[\frac{1}{N_e}\sum_{i=1}^{N_e}\left(\hat{\theta}_{k,i}-\theta_k^{(TRUE)}\right)\right]\times 100\%, \qquad (16)$$

where N_e is the number of realizations of the parameter $\hat{\theta}_k$, which has a true value (used in the simulations) of $\theta_k^{(TRUE)}$. The RMSE can be used as a measure of the spread of the distribution of the parameter estimates and is defined as[32]

$$\frac{1}{\theta_k^{(TRUE)}}\left[\frac{1}{N_e}\sum_{i=1}^{N_e}\left(\hat{\theta}_{k,i}-\theta_k^{(TRUE)}\right)^2\right]^{1/2}\times 100\%. \qquad (17)$$

It is important to note that the bias and RMSE metrics may be sensitive to outlying estimates and may hide information about the parameters' distributions. As such, we examine both the box plots for these parameter estimates and their bias and RMSE metrics.

Model 1: Mono-exponential PK, No Effect Site, Emax PD

The first PK-PD model we examine is a single compartment PK model with bolus input directly connected (ie, no effect compartment) to an Emax PD model. The model and its parameters come from Hashimoto and Sheiner.[33] This model is examined here because of its relative simplicity and its widely used structure, which makes it a good model with which to begin our investigations.

PK model: We use a single compartment model with bolus input. For the i^{th} individual, we have

$$\begin{aligned} y_i(\vec{t}_i,\vec{\theta}) &= \frac{\text{Dose}_i}{V_i}e^{-\frac{Cl_i}{V_i}\vec{t}_i}(1+\vec{\varepsilon}_i) \quad (mg/L)\\ \varepsilon_i &\sim N\left(0,\alpha^2\right)\\ Cl_i &= \beta_{pop_1}+b_{1,i} \quad (L/hr)\\ Vi &= \beta_{pop_2}+b_{2,i} \quad (L)\\ \vec{b}_i &\sim N(0,\mathbf{D}) \end{aligned} \qquad (18)$$

PD model: To describe the PD characteristics we use an Emax model. The PD model is directly connected to the PK model. For the i^{th} individual, we have

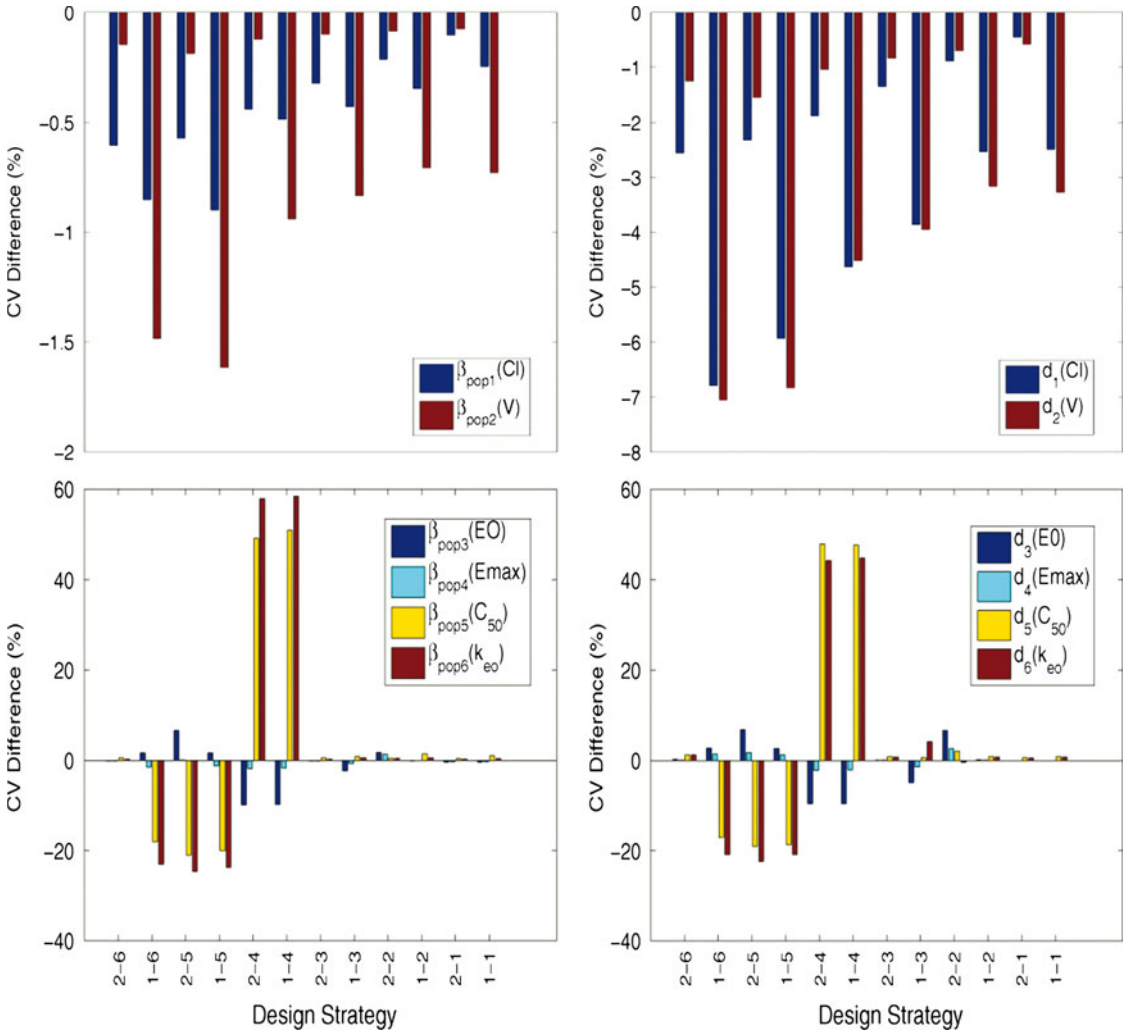

Figure 11. The percentage difference between the CVs predicted by the SIM and SEQ population optimal designs of Model 2. A negative value means the SIM design predicts a smaller CV. The top 2 plots show the PK parameter CV differences; the bottom 2 plots show the PD parameter CV differences.

$$
\begin{aligned}
\mathrm{E}_i(\vec{t}_i, \vec{\theta}) &= \mathrm{E0}_i + \frac{\mathrm{Emax}_i\, \mathrm{Cp}_i(\vec{t}_i, \vec{\theta})}{C_{50,i} + \mathrm{Cp}_i(\vec{t}_i, \vec{\theta})} + \vec{\varepsilon}_{pd,i} \\
\mathrm{Cp}_i(\vec{t}_i, \vec{\theta}) &= \frac{\mathrm{Dose}_i}{V_i} e^{-\frac{Cl_i}{V_i}\vec{t}_i} \\
\vec{\varepsilon}_{pd,i} &\sim N\left(0, \alpha_{pd}^2\right) \\
\mathrm{E0}_i &= \beta_{pop_3} + b_{3,i} \\
\mathrm{Emax}_i &= \beta_{pop_4} + b_{4,i} \\
\mathrm{C}_{50,i} &= \beta_{pop_5} + b_{5,i} \\
\vec{b}_i &\sim N(0, \mathbf{D})
\end{aligned}
\tag{19}
$$

Design specifics: The design will have 6 groups of 20 subjects each (as discussed in the section entitled "Grouping of Individuals in Population FIM Calculations"), a single dose of 1 mg, both PK and PD samples will be taken between zero and 1 hour, and model parameter values are

$$
\begin{aligned}
\vec{\theta} &= \left[\beta_{pop_1}, \beta_{pop_2}, \beta_{pop_3}, \beta_{pop_4}, \beta_{pop_5}, \right. \\
&\quad \left. d_1, d_2, d_3, d_4, d_5\right]^T \\
&= [0.5, 0.2, 1.0, 1.0, 1.0, \\
&\quad 0.01, 0.0016, 0.01, 0.09, 0.09]^T \\
\alpha^2 &= 0.15 \\
\alpha_{pd}^2 &= 0.15.
\end{aligned}
\tag{20}
$$

The design protocols are shown in Table 1.

Model 2: Mono-exponential PK, Effect Site, Emax PD

With this model, we extend Model 1 and add an effect compartment between the PK and PD models. As with Model 1, Model 2 does not specifically relate to any one drug study, although the structure of the model is commonly used in practice (see for example Colburn's treatment of acetaminophen[34]). We choose this model because it is a simple test case

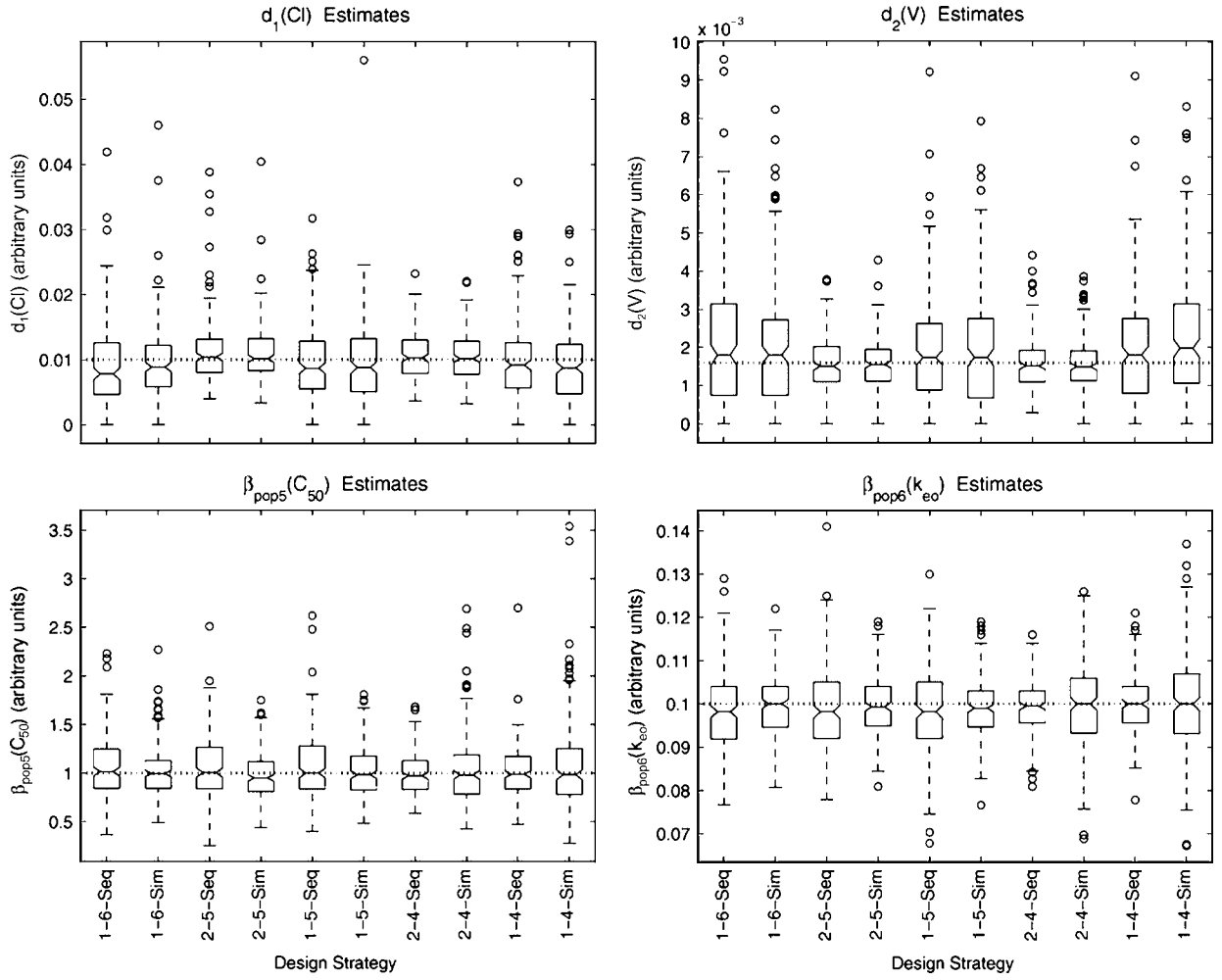

Figure 12. Box plots of parameter estimates for Model 2 using the design strategies outlined in Table 2. The dotted horizontal line is the true parameter value used in the simulations.

for simultaneous optimal design of effect compartment PK-PD experiments (with some relevance to actual PK-PD studies).

PK model: The PK model is the same as that for Model 1 (Equation 18).

PD model: The PD model is an Emax model connected to the PK model via a first order effect compartment. For the i^{th} individual, we have

$$\begin{aligned}
\mathrm{E}_i(\vec{t}_i,\vec{\theta}) &= E0_i + \frac{\mathrm{Emax}_i\,\mathrm{Ce}_i(\vec{t}_i,\vec{\theta})}{C_{50,i}+\mathrm{Ce}_i(\vec{t}_i,\vec{\theta})} + \vec{\varepsilon}_{pd,i}\\
\mathrm{Ce}_i(\vec{t}_i,\vec{\theta}) &= \frac{k_{e0,i}\mathrm{Dose}_i}{V_i k_{eo,i} - Cl_i}\left(e^{-\frac{Cl_i}{V_i}\vec{t}_i} - e^{-k_{eo,i}\vec{t}_i}\right)\\
\vec{\varepsilon}_{pd,i} &\sim N\left(0,\alpha_{pd}^2\right)\\
\mathrm{E0}_i &= \beta_{pop_3} + b_{3,i}\\
\mathrm{Emax}_i &= \beta_{pop_4} + b_{4,i}\\
\mathrm{C}_{50,i} &= \beta_{pop_5} + b_{5,i}\\
\mathrm{k}_{eo,i} &= \beta_{pop_6} + b_{6,i}\\
\vec{b}_i &\sim N(0,\mathbf{D})
\end{aligned} \tag{21}$$

Design specifics: The design will have 6 groups of 20 subjects each, a dose of 150 mg, samples for the PK measurements will be between zero and 1 hour, samples for the PD measurements will be between zero and 60 hours, and parameter values are

$$\begin{aligned}
\vec{\theta} &= \left[\beta_{pop_1},\beta_{pop_2},\beta_{pop_3},\beta_{pop_4},\beta_{pop_5},\beta_{pop_6},\right.\\
&\quad \left. d_1,d_2,d_3,d_4,d_5,d_6\right]^T\\
&= [0.5,0.2,1.0,1.0,1.0,0.1,\\
&\quad 0.01,0.0016,0.01,0.09,0.09,0.0001]^T\\
\alpha^2 &= 0.15\\
\alpha_{pd}^2 &= 0.15.
\end{aligned} \tag{22}$$

The design protocols are summarized in Table 2.

Model 3: Two-compartment PK, No Effect Site, Emax PD

In this example, we extend Model 1 by adding a second compartment to the PK model. This model and its parameters also come from Hashimoto and Sheiner.[33] As with the previous 2 models, this model does not specifically relate to

any specific study, although it is commonly used (see for example Mandema and Stanski's treatment of ketorolac[35]).

PK model: The PK model is a 2-compartment model with bolus input. For the i^{th} individual, we have

$$y_i(\vec{t}_i,\vec{\theta}) = \frac{\text{Dose}_i(\frac{Cl_{d,i}}{V_{2,i}} - \lambda_{1,i})}{V_{1,i(\lambda_{2,i}-\lambda_{1,i})}} e^{-\lambda_{1,i}\vec{t}_i} - \frac{\text{Dose}_i(\frac{Cl_{d,i}}{V_{2,i}} - \lambda_{2,i})}{V_{1,i(\lambda_{2,i}-\lambda_{1,i})}} e^{-\lambda_{2,i}\vec{t}_{i(1+\vec{\varepsilon}_i)}} (mg/L)$$

$$\lambda_{1,i} = \frac{1}{2}\left[\frac{Cl_{d,i}}{V_{1,i}} + \frac{Cl_{01,i}}{V_{1,i}} + \frac{Cl_{d,i}}{V_{2,i}} + \sqrt{\left(\frac{Cl_{d,i}}{V_{1,i}} + \frac{Cl_{01,i}}{V_{1,i}} + \frac{Cl_{d,i}}{V_{2,i}}\right)^2 - \frac{4Cl_{d,i}Cl_{01,i}}{V_{1,i}V_{2,i}}}\right] \quad (23)$$

$$\lambda_{2,i} = \frac{1}{2}\left[\frac{Cl_{d,i}}{V_{1,i}} + \frac{Cl_{01,i}}{V_{1,i}} + \frac{Cl_{d,i}}{V_{2,i}} - \sqrt{\left(\frac{Cl_{d,i}}{V_{1,i}} + \frac{Cl_{01,i}}{V_{1,i}} + \frac{Cl_{d,i}}{V_{2,i}}\right)^2 - \frac{4Cl_{d,i}Cl_{01,i}}{V_{1,i}V_{2,i}}}\right]$$

$$\begin{aligned} \varepsilon_i &\sim N\left(0,\alpha^2\right) \\ Cl_{01,i} &= \beta_{pop1} + b_{1,i} \quad (L/hr) \\ V_{1,i} &= \beta_{pop_2} + b_{2,i} \quad (L) \\ V_{2,i} &= \beta_{pop_3} + b_{3,i} \quad (L) \\ Cl_{d,i} &= \beta pop_4 + b_{4,i} \quad (L/hr) \\ \vec{b}_i &\sim N(0,\mathbf{D}) \end{aligned} \quad (24)$$

PD model: We use an Emax model to describe the PD characteristics. The PD model is directly connected to the PK model. For the i^{th} individual we have

$$E_i(\vec{t}_i,\vec{\theta}) = E0_i + \frac{\text{Emax}_i \text{C}_{\text{p}_i}(\vec{t}_i,\vec{\theta})}{C_{50,i} + C_{p_i}(\vec{t}_i,\vec{\theta})} + \vec{\varepsilon}_{pd,i}$$

$$\text{C}_{\text{p}_i}(\vec{t}_i,\vec{\theta}) = \frac{\text{Dose}_i\left(\frac{Cl_{d,i}}{V_{2,i}} - \lambda_{1,i}\right)}{V_{1,i}(\lambda_{2,i}-\lambda_{1,i})} e^{-\lambda_{1,i}\vec{t}_i} - \frac{\text{Dose}_i\left(\frac{Cl_{d,i}}{V_{2,i}} - \lambda_{2,i}\right)}{V_{1,i}(\lambda_{2,i}-\lambda_{1,i})} e^{-\lambda_{2,i}\vec{t}_i} \quad (25)$$

$$\begin{aligned} \vec{\varepsilon}_{pd,i} &\sim N\left(0,\alpha^2_{pd}\right) \\ E0_i &= \beta_{pop5} + b_{5,i} \\ \text{Emax}_i &= \beta_{pop6} + b_{6,i} \\ C_{50,i} &= \beta_{pop7} + b_{7,i} \\ \vec{b}_i &\sim N(0,\mathbf{D}) \end{aligned}$$

Design specifics: The design will have 6 groups of 20 subjects each, a dose of 1 mg, samples will be between zero and 1 hour, and parameter values are

$$\begin{aligned} \vec{\theta} &= [\beta_{pop_1},\beta_{pop_2},\beta_{pop_3},\beta_{pop_4},\beta_{pop_5},\beta_{pop_6},\beta_{pop_7}, d_1,d_2,d_3,d_4,d_5,d_6,d_7]^T \\ &= [0.6, 0.15, 0.15, 0.6, 1.0, 1.0, 1.0, \\ &\quad 0.0144, 0.0009, 0.0009, 0.0144, 0.01, 0.09, 0.09]^T \\ \alpha^2 &= 0.15 \\ \alpha^2_{pd} &= 0.15. \end{aligned} \quad (26)$$

The design protocols are shown in Table 3.

Model 4: PK-PD for the Oral Dosing of Theophylline

In this model we describe the PK-PD for the oral dosing of theophylline, an anti-asthmatic agent. We choose this model because it affords us the opportunity to extend the results

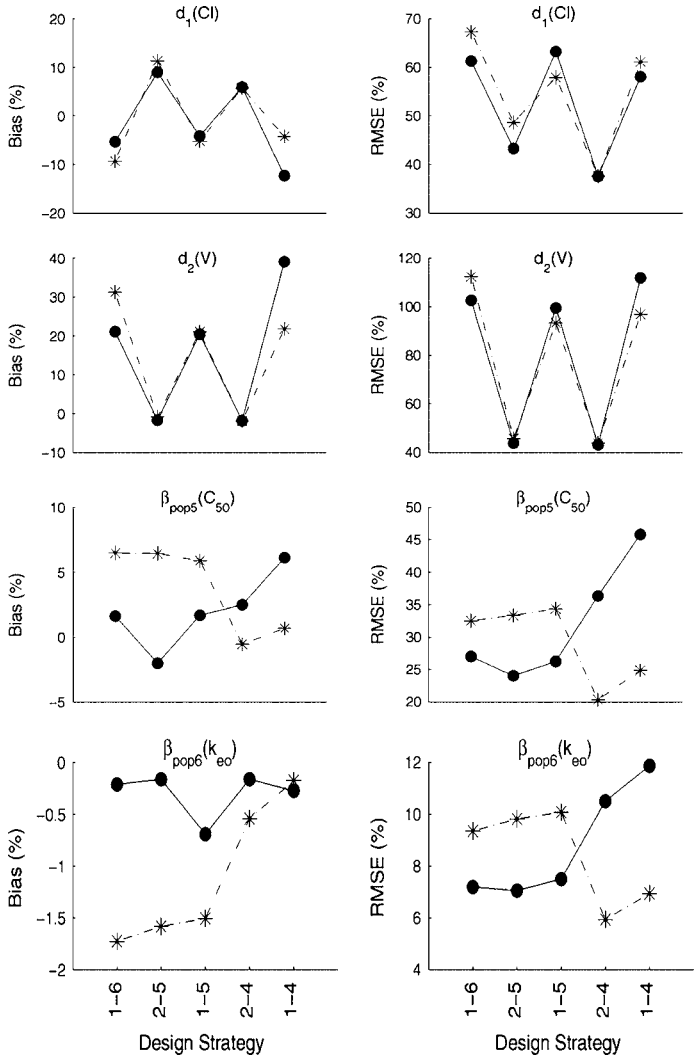

Figure 13. The percentage bias and RMSE for parameters in Model 2. Design methods are outlined in Table 2. (*)- SEQ population optimal designs, (•)- SIM population optimal designs.

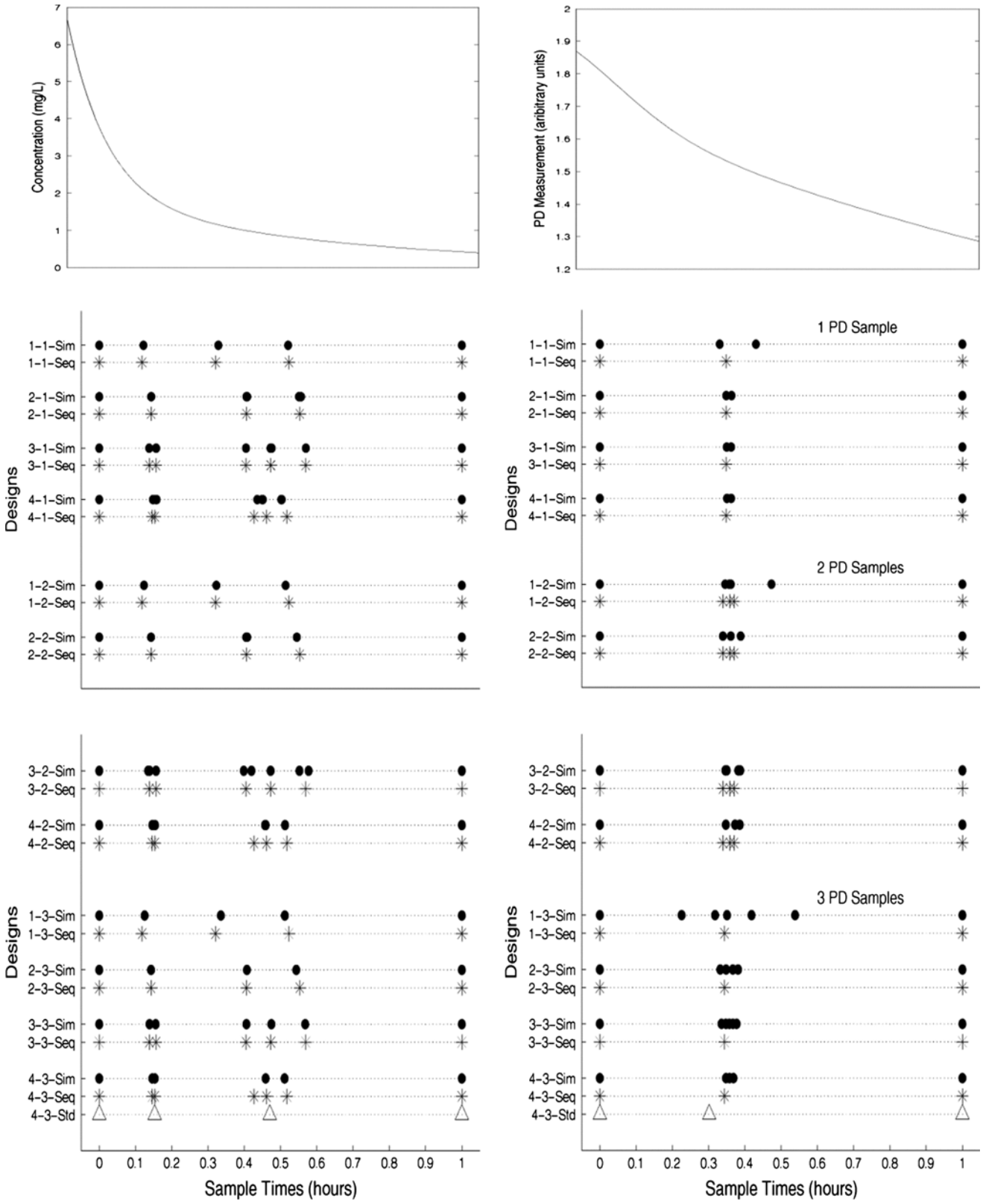

Figure 14. Sampling times for each design considered in Model 3. For each design, all sample times from all individuals are plotted together on one line. The left figure shows the PK sample times and the right figure shows the PD sample times. (Δ)- SEQ STD optimal times, (*)- SEQ population optimal times, (•)- SIM population optimal times. The population model mean PK and PD response curves are shown above their respective sampling times.

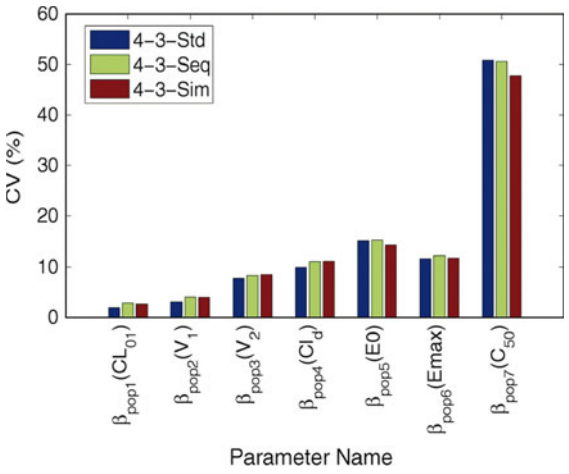

Figure 15. Model 3 CVs for the SIM, SEQ, and STD designs with 4 PK and 3 PD samples per individual. No major differences are evident.

obtained in previous work[24] for the PK optimal designs of theophylline. In addition, the PD model described below is quite complex and has been used for real data, and, as such, it is a good test for the methods we have developed thus far.

PK model: The PK for Model 4 is well described by a one-compartment model with linear absorption and constant measurement error variance. We define the model for the i^{th} individual as:

$$\begin{aligned}
\vec{Y}_i\left(\vec{t}_i,\vec{\theta}\right) &= \frac{\text{Dose}_i k_{21,i} k_{02,i}}{Cl_i(k_{21,i}-k_{02,i})}\left(e^{-k_{02,i}\vec{t}_i}-e^{-k_{21,i}\vec{t}_i}\right) \\
&\quad + \varepsilon_i \quad (mg/L) \\
\varepsilon_i &\sim N(0,\alpha^2) \quad (mg/L) \\
k_{21,i} &= \beta_{pop_1} e^{b_{1,i}} \quad (hr^{-1}) \\
k_{02,i} &= \beta_{pop_2} e^{b_{2,i}} \quad (hr^{-1}) \\
Cl_i &= a_i \beta_{pop_3} e^{b_{3,i}} \quad (L/hr) \\
\vec{b}_i &\sim N(0,\mathbf{D}) \\
\frac{\text{Dose}_i}{a_i} &\in [3.10, 5.86] \quad (mg/kg)
\end{aligned} \tag{27}$$

where a_i is the weight of individual i and Cl_i is the clearance from the accessible compartment. The assumed true parameter values for this model are estimated using the FO method in NONMEM and the data set from Beal and Sheiner.[36]

PD model: The PD model we examine is taken from Holford et al.[37] This model describes the PD measurement of peak expiratory flow rate (PEFR) as a direct effect model (ie, they assume that the plasma is the effect site; thus there is no effect compartment). The model makes the assumption that the PEFR is influenced by both the theophylline concentration in the blood and a hypothetical broncho-constrictor factor (BCF). For an individual i, the effect of the BCF on the PEFR is

$$\begin{aligned}
\text{PEFR}_{BCF,i}\left(\vec{t}_i,\vec{\theta}\right) &= \text{Nml}_i\left(1-\left[\frac{\text{BCF}_i(\vec{t}_i,\vec{\theta})}{\text{BCF}_i(\vec{t}_i,\vec{\theta})+C_p50_i}\right]\right) \\
\text{BCF}_i(\vec{t}_i,\vec{\theta}) &= C_p50_i \\
&\quad \times (\text{Nml}_i/Bse_i - 1)e^{-ln2/T\,50_{BCF,i}\vec{t}_i}
\end{aligned} \tag{28}$$

where Bse_i is the baseline PEFR for individual i during an asthma attack and Nml_i is the baseline PEFR for that individual in the normal state. The effect of theophylline on the PEFR is

$$\begin{aligned}
\text{PEFR}_{THEO,i}\left(\vec{t}_i,\vec{\theta}\right) &= (\text{Nml}_i - \text{PEFR}_{BCF,i}\left(\vec{t}_i,\vec{\theta}\right)) \\
&\quad \times \frac{C_p(\vec{t}_i,\vec{\theta})^h}{C_p(\vec{t}_i,\vec{\theta})^h + C_p50_i^h} \\
C_p(\vec{t}_i,\vec{\theta}) &= \frac{\text{Dose}_i k_{21,i} k_{02,i}}{Cl_i(k_{21,i}-k_{02,i}} \\
&\quad \times \left(e^{-k_{02,i}\vec{t}_i} - e^{-k_{21,i}\vec{t}_i}\right) \quad (mg/L)
\end{aligned} \tag{29}$$

The overall effect on PEFR is thus

$$\begin{aligned}
\text{PEFR}_i\left(\vec{t},\vec{\theta}\right) &= \Big[\text{PEFR}_{BCF,i}\left(\vec{t}_i,\vec{\theta}\right) \\
&\quad + \alpha_{theo,i}\text{PEFR}_{THEO,i}\left(\vec{t}_i,\vec{\theta}\right)\Big] \\
&\quad \times (1+\vec{\varepsilon}_{pd,i}) \quad (L/min) \\
\vec{\varepsilon}_{pd,i} &\sim N\left(0,\alpha_{pd}^2\right) \\
\text{Bse}_i &= \beta_{pop_4} e^{b_{4,i}} \quad (L/min) \\
\text{Nml}_i &= \beta_{pop_5} e^{b_{5,i}} \quad (L/min) \\
T50_{BCF,i} &= \beta_{pop_6} e^{b_{6,i}} \quad (1/min) \\
C_p50_i &= \beta_{pop_7} e^{b_{7,i}} \quad (mg/L) \\
\alpha_{theo,i} &= \beta_{pop_8} \\
h &= \beta_{pop_9} \\
\vec{b}_i &\sim N(0,\mathbf{D})
\end{aligned} \tag{30}$$

For more information on this interesting model please see Holford et al.[37]

Design specifics: The assumed true parameter values for this model are

$$\begin{aligned}
\vec{\varphi} &= \left[\beta_{pop_1},\beta_{pop_2},\beta_{pop_3},\beta_{pop_4},\beta_{pop_5},\beta_{pop_6},\beta_{pop_7},\right. \\
&\quad \left.\beta_{pop_8},\beta_{pop_9},d_1,d_2,d_3,d_4,d_5,d_6,d_7\right]^T \\
&= [2.71, 0.0763, 0.0373, 133, 477, 16, 11, 0.518, 2.13, \\
&\quad 0.784, 0.0185, 0.0428, 0.14444, 0.0484, \\
&\quad 0.6561, 0.6084]^T \\
\alpha^2 &= 0.419 \\
\alpha_{pd}^2 &= 0.04.
\end{aligned} \tag{31}$$

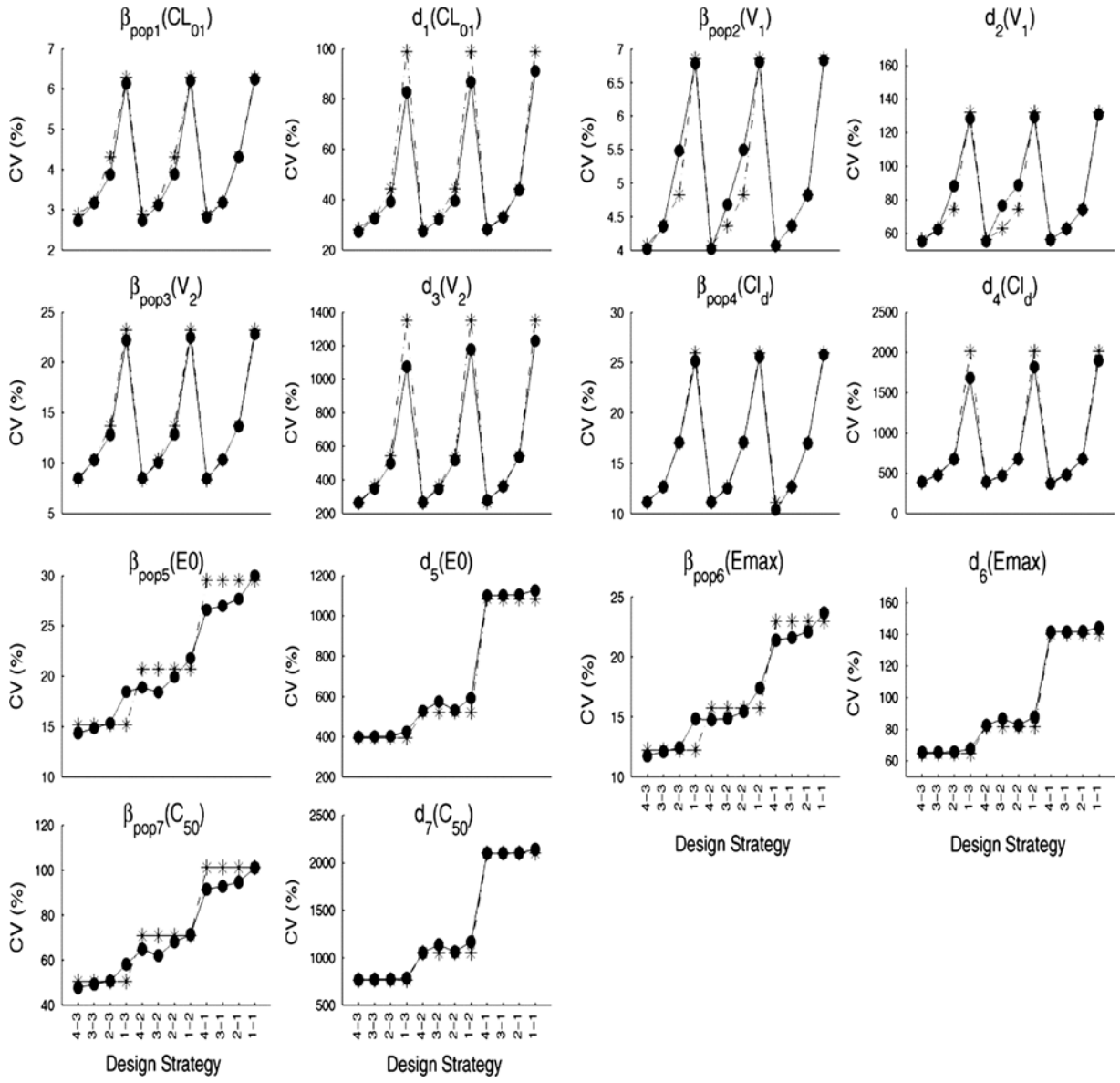

Figure 16. Model 3 CVs for the SIM, SEQ, and STD designs with 4 PK and 3 PD samples per individual. No major differences are evident.

To be consistent with the design setup used in Beal and Sheiner's theophylline PK study,[36] we assume that there are 12 individuals in the study with an oral dose of the drug at time zero. Each sample time for the PK model will be within 24 hours of dosage, sample times for the PD model will be between zero and 1 week. The design protocols are shown in Table 4.

RESULTS

Model 1: Mono-exponential PK, No Effect Site, Emax PD

Optimal Designs

The computed optimal design sample times (for all individuals and for each design outlined in Table 1) are shown in Figure 1. These conglomerated plots give a sense of how the design times are distributed. We see that there is relatively little difference between the sampling times for the various designs, although there does appear to be a slight shift in sampling times for the PD measurement at roughly 0.6 hours. Because all of the designs are quite similar, we expect there to be relatively little difference between the design results. In general the number of observations contained in each point of these plots is roughly equivalent within a design. For example, in the 2-2-SIM design there appear to be 4 distinct sampling times, with 2 PD samples per individual and 6 groups of 20 subjects; each point in this design represents ~30 sampling times. This equivalence seems to hold roughly true for each model explored in this work. It would be interesting to see how these distributions change between designs, but we did not investigate this aspect of the design in detail here.

Figure 2 compares the asymptotic CVs for the 3_{pk}-6_{pd} designs where all 3 design types could be used. The difference

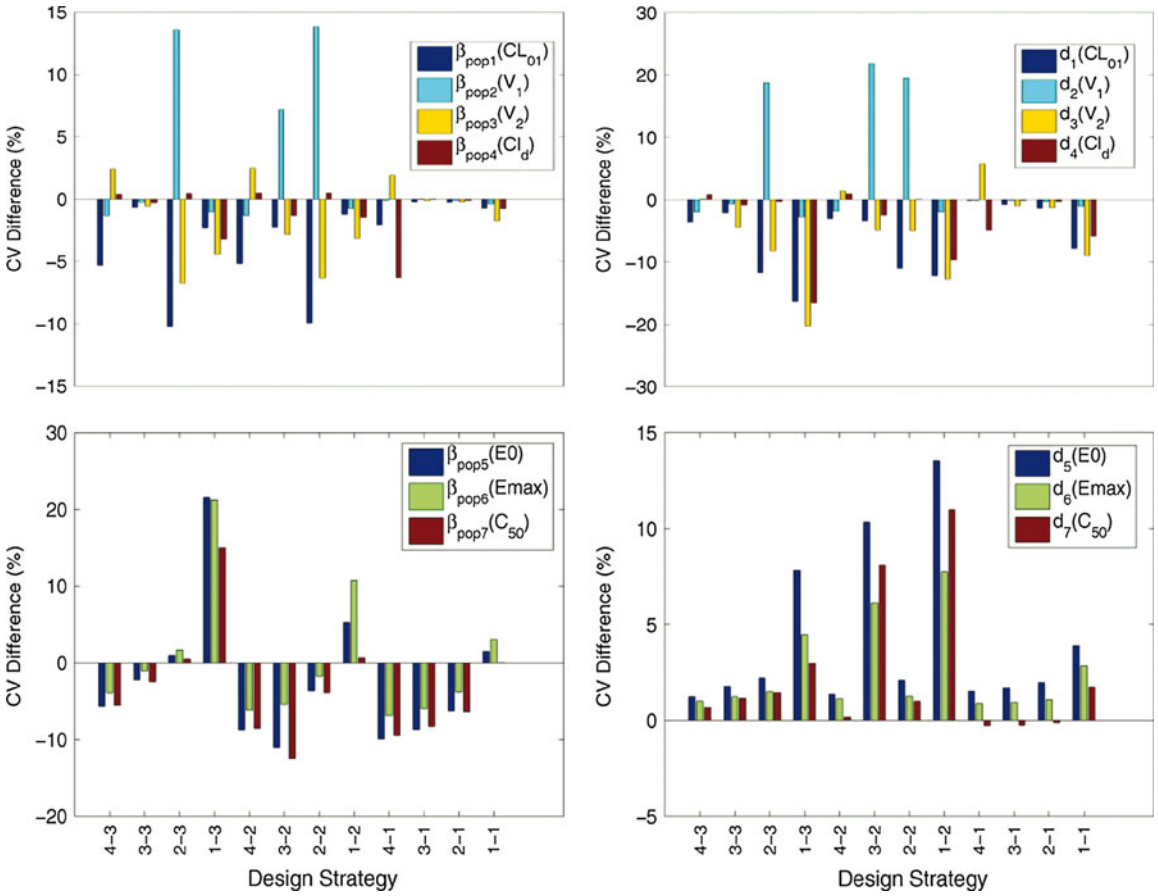

Figure 17. The percentage difference between the CVs predicted by the SIM and SEQ population optimal designs of Model III. A negative value means the SIM design predicts a smaller CV. The top 2 plots show the PK parameter CV differences; the bottom 2 plots show the PD parameter CV differences.

between the STD and SEQ designs are relatively minor, with the SIM designs predicting CVs for a_{pop3}, β_{pop4}, and β_{pop5} that are smaller by roughly 20% to 25%.

Figure 3 shows the asymptotic CVs predicted by the optimal FIM for the SIM and SEQ population designs. The pattern we would expect to see (and actually do see) in this figure is a general increase in CV for the PD parameters, as the designs move from 3 PD samples to 2 and then to 1 PD sample. Similarly, we expect to see an increase in the CV of the PK parameters as we move from designs with 2 PK samples to designs with 1 PK sample, and then a decrease as we go back to 2 samples. From this figure, we again see surprising improvements (given how similar the sample times are between the various designs) in the SIM CVs for the PD fixed effects relative to the SEQ designs (β_{pop3}, β_{pop4}, and β_{pop5} in Figure 3). We also note that many of the random effect parameters (particularly d_3 and d_5) are very poorly estimated by all designs. This indicates the inadequacy of these designs to identify these parameters, which could be a result of the small population sample size.

The percentage difference between the SIM and SEQ population designs is shown in Figure 4. The percentage differences show that, for the PD fixed effects β_{pop3}, β_{pop4}, and β_{pop5}, the predicted CVs for the SIM designs are approximately 20% to 25% better than the SEQ designs. Given the large predicted CVs for the PD random effects, we assume that the percentage differences shown for these parameters are relatively insignificant from a practical standpoint.

Especially of note for the PK CV differences is the marked improvement of the SIM designs when the designs have many PD samples but only 1 PK sample. In Figure 4 we can see that for both the 1_{pk}-3_{pd} designs and the 1_{pk}-2_{pd} designs, the difference between the SIM and SEQ designs is much greater than for the other design strategies. This finding seems to indicate that the PD measurements in a SIM design can help mitigate the poor estimation of PK parameters that we see in low sample number designs.[24] We also note that the SIM designs consistently predict better (although by just 2%-10%) CVs for the PK parameter values.

Simulation Studies

To investigate further the CV differences we have seen, we evaluate the designs through 200 simulation/estimation experiments. Some of these experiments resulted in poor

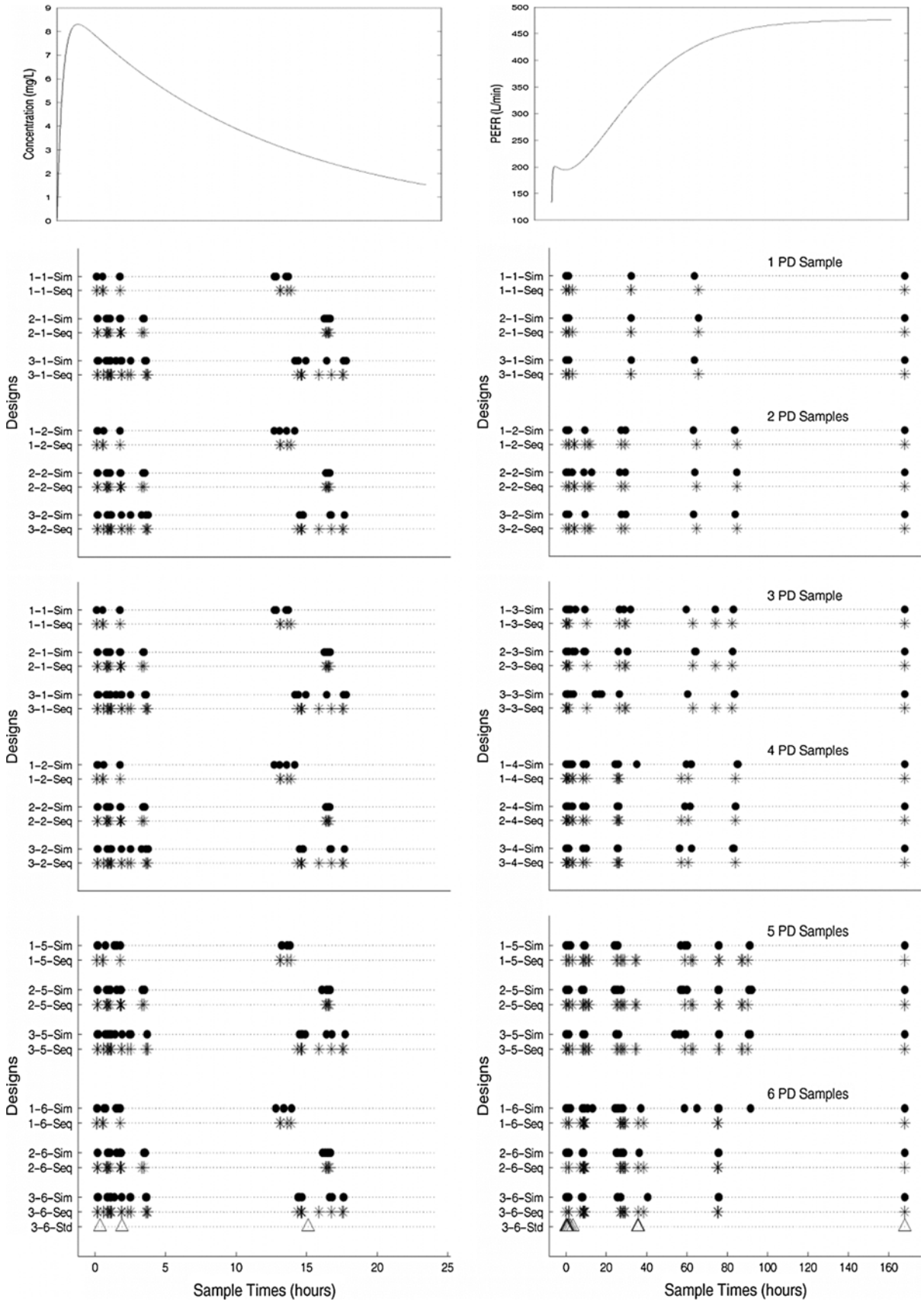

Figure 18. Sampling times for each design considered in Model 4. For each design, all sample times from all individuals are plotted together on one line. The left figure shows the PK sample times and the right figure shows the PD sample times. (Δ)- SEQ STD optimal times, (*)- SEQ population optimal times, (•)- SIM population optimal times. The population model mean PK and PD response curves are shown above their respective sampling times.

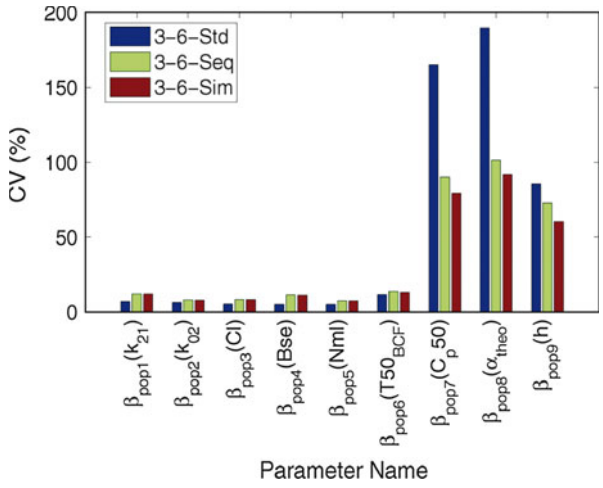

Figure 19. CVs for the SIM, SEQ, and STD 3_{pk}-6_{pd} designs considered in Model 4.

parameter estimates (due mostly to estimation termination, or estimated parameter values that were on a search region boundary) and were discarded in subsequent analysis. Figure 5 shows the number of simulation studies used to compare the various designs. The figure also gives an idea of the robustness of the designs in parameter estimation; many discarded simulations indicate a lack of robustness. The designs for Model 1 appear to be fairly robust.

The estimated parameter values for d_2, β_{pop3}, β_{pop4}, and β_{pop5} are shown in Figure 6 and their bias and RMSE are shown in Figure 7. We examine these parameters values via our simulation/estimation procedure because they had the largest CV differences in the asymptotic FIM comparisons. We note the high degree of bias in the β_{pop5} parameter estimates, which are perhaps not surprising given that the FIM predicted CV values for this parameter were so high (see Figure 3) and that the C_{50} parameter is often very hard to estimate, especially in designs with very few samples per subject. It is clear from the box plots and RMSE calculations that the variance of the parameter estimates increases as the total number of PK and PD samples decreases. It also appears that, for most designs, the difference in variance is small. For design strategy 1_{pk}-1_{pd}, the design appears to be inadequate to accurately determine model parameters. The differences between the SIM and SEQ designs seen in asymptotic FIM predictions are not as evident in the simulation/estimation studies.

Model 2: Mono-exponential PK, Effect Site, Emax PD

Optimal Designs

We computed optimal designs for each of the design protocols shown in Table 2. The sample times for all individuals for each design (Figure 8) reveal no difference between designs in the PK samples. For the PD sample times, there seems to be an increase in spread around 30 to 45 hours as the total number of samples in the design increases.

Figure 9 compares the asymptotic CVs for the designs where all 3 design types could be used. There are differences between the designs in the β_{pop5} and β_{pop6} parameters. However, there does not appear to be a clear pattern to these differences. Asymptotic CVs of the random effect variances are not compared because the STD (non-population-based) design method does not incorporate them for determination of the design.

Figure 10 shows the asymptotic CVs predicted by the optimal FIM for the SIM and SEQ population designs. As with Figure 9 we again see discrepancies between the designs in predicted CVs for the C_{50} and k_{eo} parameters (β_{pop5}, d_5 and β_{pop6}, d_6, respectively). There is a consistent pattern in which the SIM designs are better for the 1-6, 2-5, and 1-5 protocols, while the SEQ designs are better for the 2-4 and 1-4 protocols. It is not clear why this pattern emerges, although we note that the largest difference between design points in Figure 8 is also within these same designs. As with Model 1, the designs explored for this model predict very large CVs for many of the PD random effects (d_3-d_6). This finding indicates an inadequacy of these designs to estimate these parameters.

The percentage difference between the SIM and SEQ population designs ($(CV_{sim} - CV_{seq})/CV_{seq}$) is shown in Figure 11. We see up to a 55% difference in estimating the CVs for 2 of the PD fixed effect parameters. Given the large predicted CVs for the PD random effects, we assume that the percentage differences shown are relatively insignificant (the CVs are all actually unacceptable).

The percentage differences for the PK parameter CVs show that, as with Model 1, the SIM designs consistently predict better (although only by 0.1-7%) CVs for the PK parameter values. It is again interesting to note that the designs with many PD samples and only 1 PK sample show a much greater difference (in favor of the SIM designs) than do the other design strategies, pointing to the potential value added by PD samples to PK estimation.

Simulation Studies

To further investigate the CV differences seen between the SEQ and SIM CVs for some of the PD fixed effects and the PK parameters, we evaluate the designs that show the largest difference through simulation/estimation experiments. For each design considered, the estimated parameter values for d_1, d_2, β_{pop5}, and β_{pop6} for 200 simulations are shown in Figure 12, and the bias and RMSE of these parameter estimates are shown in Figure 13. For this model, no estimated parameter values were discarded, indicating a more robust model than Model 1.

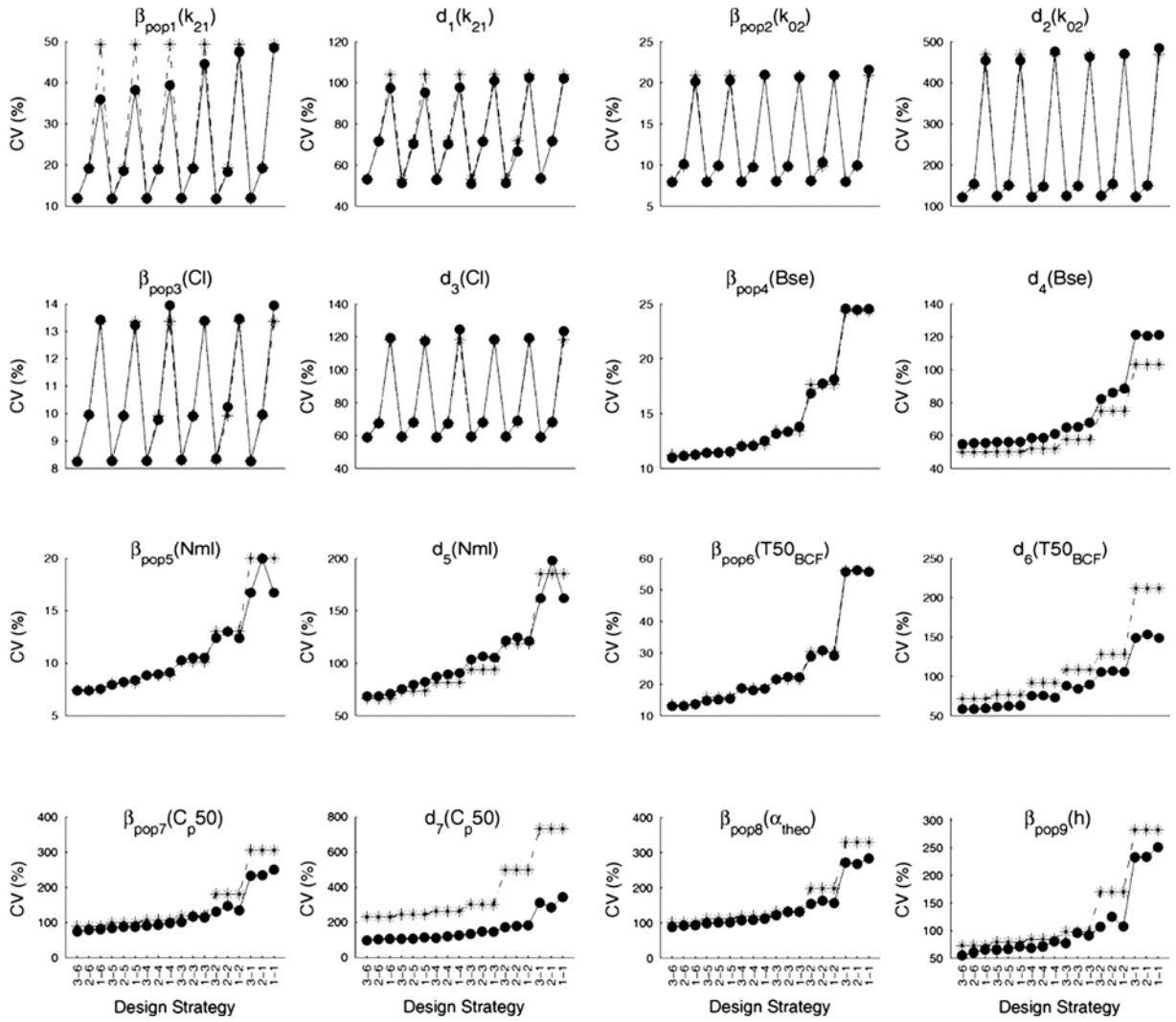

Figure 20. CVs for the SIM and SEQ population designs considered in Model 4. (*)- SEQ population optimal designs, (•)- SIM population optimal designs.

For the PK parameters shown (d_1 and d_2) there are clear differences in variance between design strategies (refer to the box plots and RMSE). However, there is very little difference between the SIM and SEQ designs with the same design strategy (ie, the same number of PK and PD samples). Differences between the SEQ and SIM designs are evident for the PD parameters shown (β_{pop5} and β_{pop6}), with the same pattern seen with the FIM asymptotic predictions. For some design strategies the variance (RMSE and box plots) is better for the SEQ design, and for other design strategies the variance is better for the SIM design. It is not clear why the designs have this characteristic and more investigation is needed to elucidate the differences between the SIM and SEQ designs in this case.

Model 3: Two Compartment PK, No Effect Site, Emax PD

Optimal Designs

We computed optimal designs for each of the design protocols shown in Table 3. The sample times for all individuals for each design (Figure 14) reveal little difference between designs in the PD samples. For the PK sample times there seems to be much variation for the samples between 0.3 and 0.7 hours. However, when both designs have the same number of PK and PD samples, there is little difference between the SIM and SEQ design times.

Figure 15 reveals little difference between the asymptotic CVs for the designs where all 3 design types could be used.

Figure 16 shows the asymptotic CVs predicted by the optimal FIM for the SIM and SEQ population designs. We see few differences between the designs. The designs explored for this model predict very large CVs for many of the random effects ($\vec{d}$). This indicates the inadequacy of these designs to estimate these parameters.

The percentage difference between the SIM and SEQ population designs is shown in Figure 17. The main feature this result seems to show is the slight change for the worse in

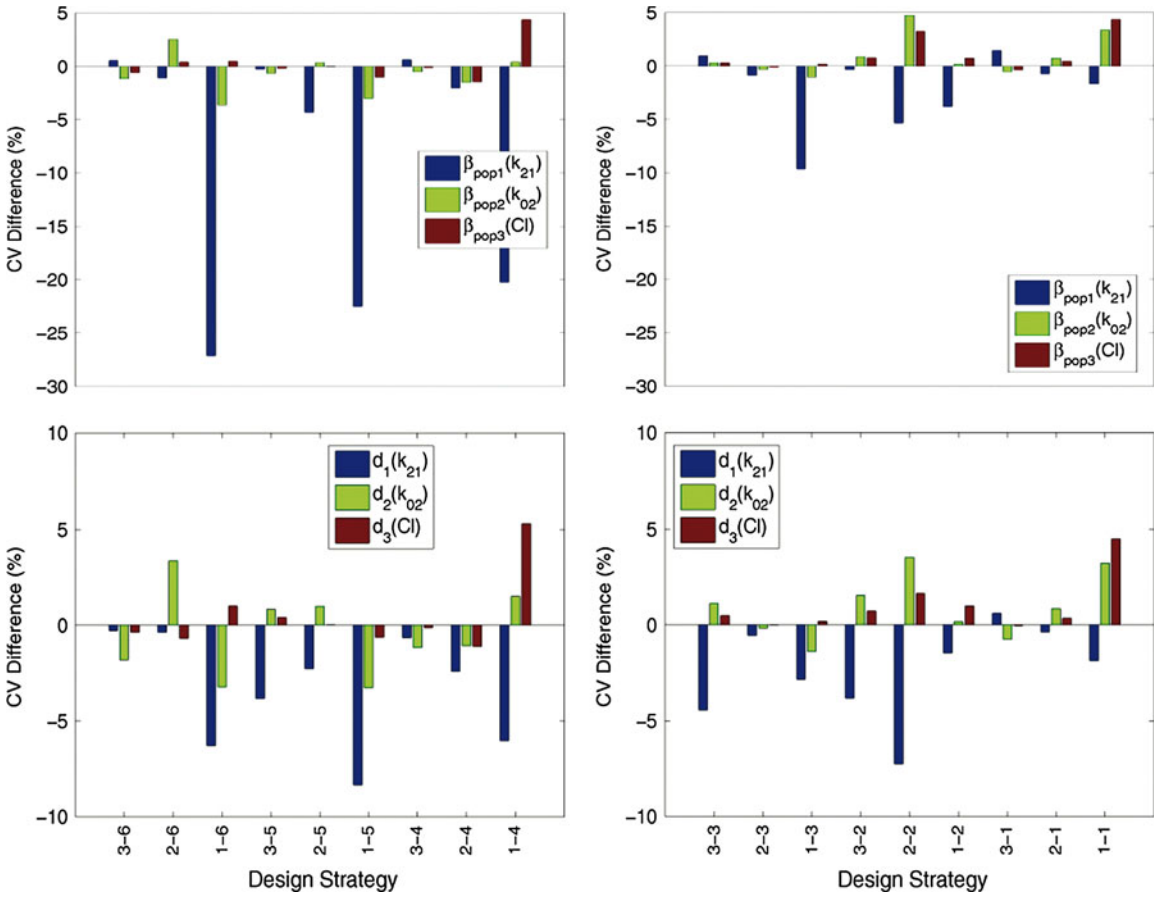

Figure 21. The Model 4 PK parameter percentage difference between the CVs predicted by the SIM and SEQ population optimal designs. A negative value means the SIM design predicts a smaller CV. The top 2 plots show the PK fixed effects CV differences; the bottom 2 plots show the PK random effects CV differences.

estimating the PD random effects using SIM designs. However, given the large predicted CVs for the PD random effects, we assume that the percentage differences shown are relatively insignificant. As a general comment, we believe that the poor estimate quality for the PD parameters in most of the models we have selected can be ascribed to the single-dose designs we have chosen to evaluate. Although not within the scope of the present work, we can speculate that a multiple-dose approach in which the PD (and PK) profile is measured for many inputs would provide a better chance to improve the quality of the PD parameter estimates.

Simulation Studies

Because there does not seem to be any discernable difference between the SIM and SEQ designs, we stopped here in our analysis of this model, without further simulation studies.

Model 4: PK-PD for the Oral Dosing of Theophylline

Optimal Designs

We computed optimal designs for each of the design protocols shown in Table 4. The sample times for all individuals for each design (Figure 18) reveal little difference between designs within each design strategy (ie, when all designs have the same number of PK and PD samples). However, there does appear to be quite a bit of variation between design strategies.

Figure 19 compares the asymptotic CVs for the designs in which all 3 design types could be used. What stands out in this analysis is the poor CV prediction using the STD non-population-based optimal design for 3 of the PD fixed effects β_{pop7}, β_{pop8}, and β_{pop9}. There also seems to be a large difference between the SIM and SEQ CV prediction for these parameters; the SIM design yields much better results. We note, however, that the STD design does seem to do somewhat better than the SEQ or SIM designs in predicting the other fixed effect parameters in the model (β_{pop1}-β_{pop6}).

Figure 20 shows the asymptotic CVs predicted by the optimal FIM for the SIM and SEQ population designs. From this figure we again see that the SIM CVs for 3 of the PD fixed effects, β_{pop7}, β_{pop8}, and β_{pop9} are predicted to be smaller than in the SEQ designs. We also see some other differences. First, again we note the PK CV differences, especially in designs with high PD sample numbers and 1

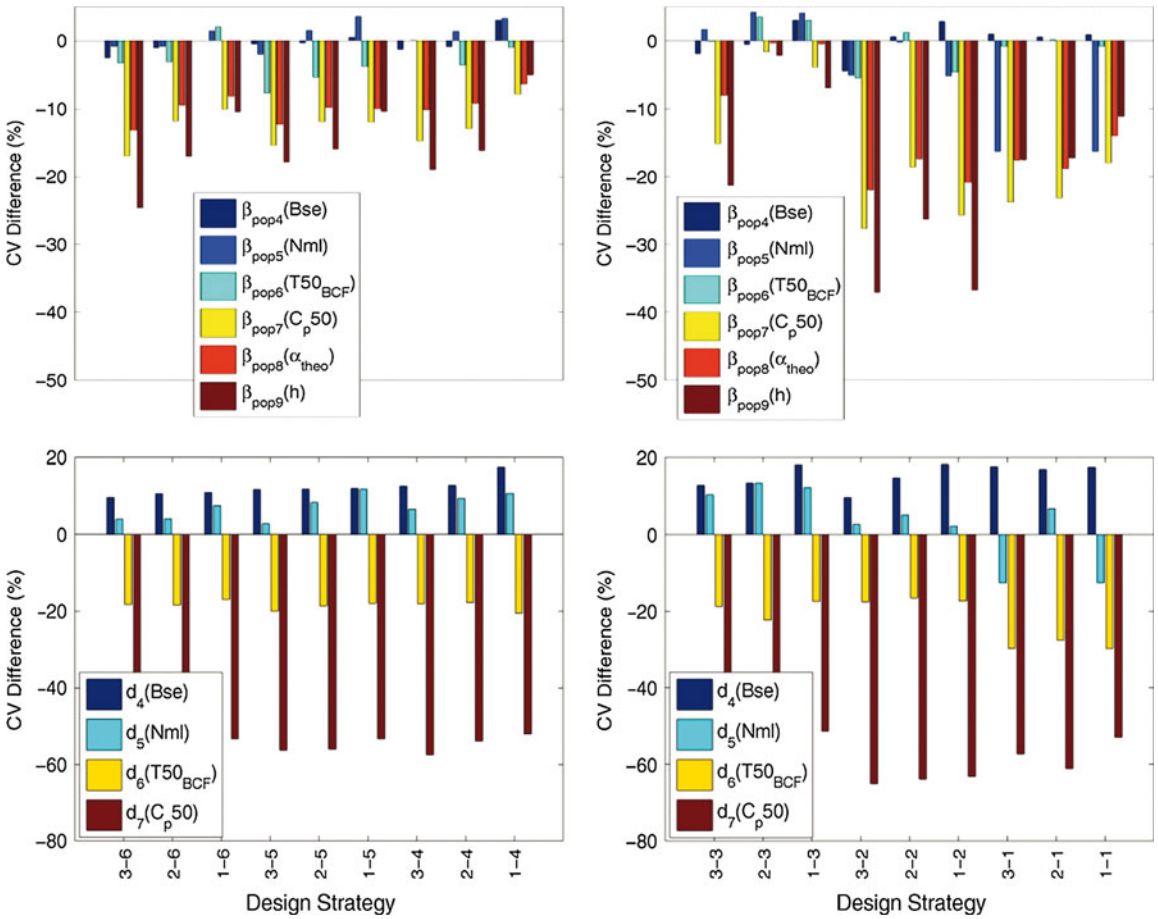

Figure 22. The Model 4 PD parameter percentage difference between the CVs predicted by the SIM and SEQ population optimal designs. A negative value means the SIM design predicts a smaller CV. The top 2 plots show the PD fixed effects CV differences; the bottom 2 plots show the PD random effects CV differences.

PK sample. Second, we note the apparent improvement of some PD random effect CVs in the SEQ designs, compared with the SIM designs. However, we also note that many of the random effect parameters (particularly d_7) are very poorly estimated by all designs. This may indicate the inadequacy of the sample size to identify these parameters.

The percentage difference between the SIM and SEQ population designs is shown in Figures 21 and 22. For the PK parameters (Figure 21), we see very clearly the same effect as in Models 1 and 2; namely, that the designs with many PD samples and only 1 PK sample show a much greater difference (in favor of the SIM designs) than do the other design strategies. In this model the effect is especially clear for β_{pop1} (in particular, design strategies 1-6, 1-5, 1-4, and 1-3 compared with the rest of the design strategies).

For the PD parameters (Figure 22), we see that the CVs for the fixed effects all generally favor the SIM design, although, in general, only slightly. The PD random effect parameters are a mixed bag; the largest difference is for the parameter with the largest predicted CVs

Simulation Studies

To investigate further the CV differences seen between the SEQ and SIM CVs we evaluate the designs that appear to show a difference through simulation. For each design considered, 200 simulation/estimation experiments were performed. Figure 23 shows the number of usable parameter estimates from the 200 simulations attempted for each design. It is clear this model had some problems estimating the simulated data, which demonstrates that this model is less robust than the other models considered in this work. However, this lack of robustness is not unexpected; in their study describing model development, Holford et al[37] make repeated reference to the numerical difficulties they encountered.

The estimated parameter values for β_{pop1}, d_4, β_{pop7}, d_7, β_{pop8}, and β_{pop9} are shown in Figure 24, and the bias and RMSE for these parameters are shown in Figure 25. Overall, it is clear that at very low sample numbers the designs are inadequate to estimate the parameter values (see, for example, the bias and RMSE plots for d_7, design strategy 1_{pk}-2_{pd}, where the

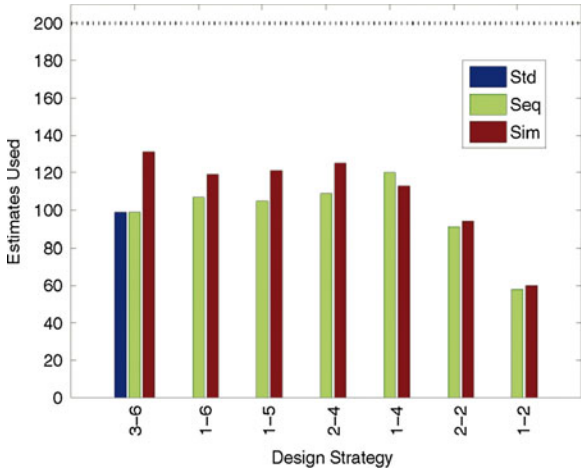

Figure 23. The number of simulation/estimation studies used to compare the various designs for model IV. Two hundred simulations were attempted for all designs, but some parameter estimates were subsequently thrown out.

values are so much larger than the other design protocols that we have chosen not to plot them on the same graphs). However, most of the other designs seem roughly equivalent in estimating parameter values. This includes population designs that have fewer samples per subject than theoretically allowed by the STD SEQ design (3-6-Std).

More specifically, the difference seen in the asymptotic FIM predictions between β_{pop7}, β_{pop8}, and β_{pop9} in the various 3_{pk}-6_{pd} design strategies (standard sequential, population SEQ, and SIM sequential) are not evident in the simulation studies. Also not confirmed in the simulation studies are the differences seen in the asymptotic FIM predictions between the SIM and SEQ variances for parameters β_{pop1}, β_{pop7}, β_{pop8}, and β_{pop9}. The simulation studies do reveal that the SIM designs do better than the SEQ designs in estimating d_7. However, the parameter is still very poorly estimated for all design strategies and the improvements may be practically inconsequential.

DISCUSSION

In this work, we have compared SIM population PK-PD D-optimal designs to SEQ population designs and STD (no random population effects) SEQ designs. We have found that, with the same number of samples per individual, there is very little difference between these 3 methods of optimal design. This indicates to us that population design, and especially SIM population design, may not be particularly effective for experiments with the number of individual PK and PD samples above the theoretical limit of STD non-population-based designs (ie, the number of fixed effects in the PK-PD model). In our view, the big benefit of population optimal design comes from the ability to design experiments with fewer samples than there are fixed effects in the model.

Our results indicate that both SIM and SEQ designs work equally well in designing these low sample number experiments. Only when very few samples per subject are used (1 PK sample and 1 PD sample, for example) will these design methods have difficulty. There is some scant evidence in this work to suggest that SIM designs may outperform SEQ designs in certain cases (Model 4, parameter d_7; Model 2, some design strategies). However, there were no clear differences, and it is not obvious to us how to project these small differences into some general rule.

Often, the predicted CVs from the FIM for the SIM optimal designs did appear to do better than the SEQ designs, especially for the estimation of the PK parameters and the PD parameter fixed effects. However, when we tested these differences in simulation/estimation studies, both design strategies appeared to do just as well (or just as poorly for the PD random effects, likely owing to the fact that only one dose level was used in the experiments). The disappearance of these differences is likely because the inverse of the FIM is only an *asymptotic* approximation to the covariance matrix of the estimated parameters. In the studies examined in this work we are, in fact, far away from the assumed asymptotic limit of many individuals with many samples per individual. As a result, it is important to test the results that the FIM provides through simulation, and to not just rely on the FIM for design inference.

It is worth noting that the SIM designs were expected to result in less accurate PD parameter variances because the PK parameters in the PD model were not assumed to be known (as was the case with SEQ designs). Our results do not support this prediction. Both the SIM and SEQ designs had very similar results for the PD parameters.

We also note that, for both SIM and SEQ design techniques, if only 1 PD (or PK) measurement is made then the resulting variances for the PD (or PK) parameters will be much worse than for designs with more PD (or PK) measurements. This appears to support an observation we made in a previous study[24] that 1 sample per individual in a PK experiment may lead to an inadequate design protocol. Although 1 PD (or PK) sample per individual and many PK (or PD) samples per individual may be adequate, there is significant improvement in the PD (or PK) parameter variances if more PD (or PK) samples are taken.

Our results suggest that SIM and SEQ population design approaches are equally effective when using models in which the between-subject correlation between the PK and PD parameters is not explicitly accounted for in **D** (we assumed that this matrix, the variance of the random effects, was diagonal; in NONMEM this means a diagonal omega matrix). It would be interesting to explore the case in which PK parameters are directly correlated with PD parameters in terms of population variability. A reviewer

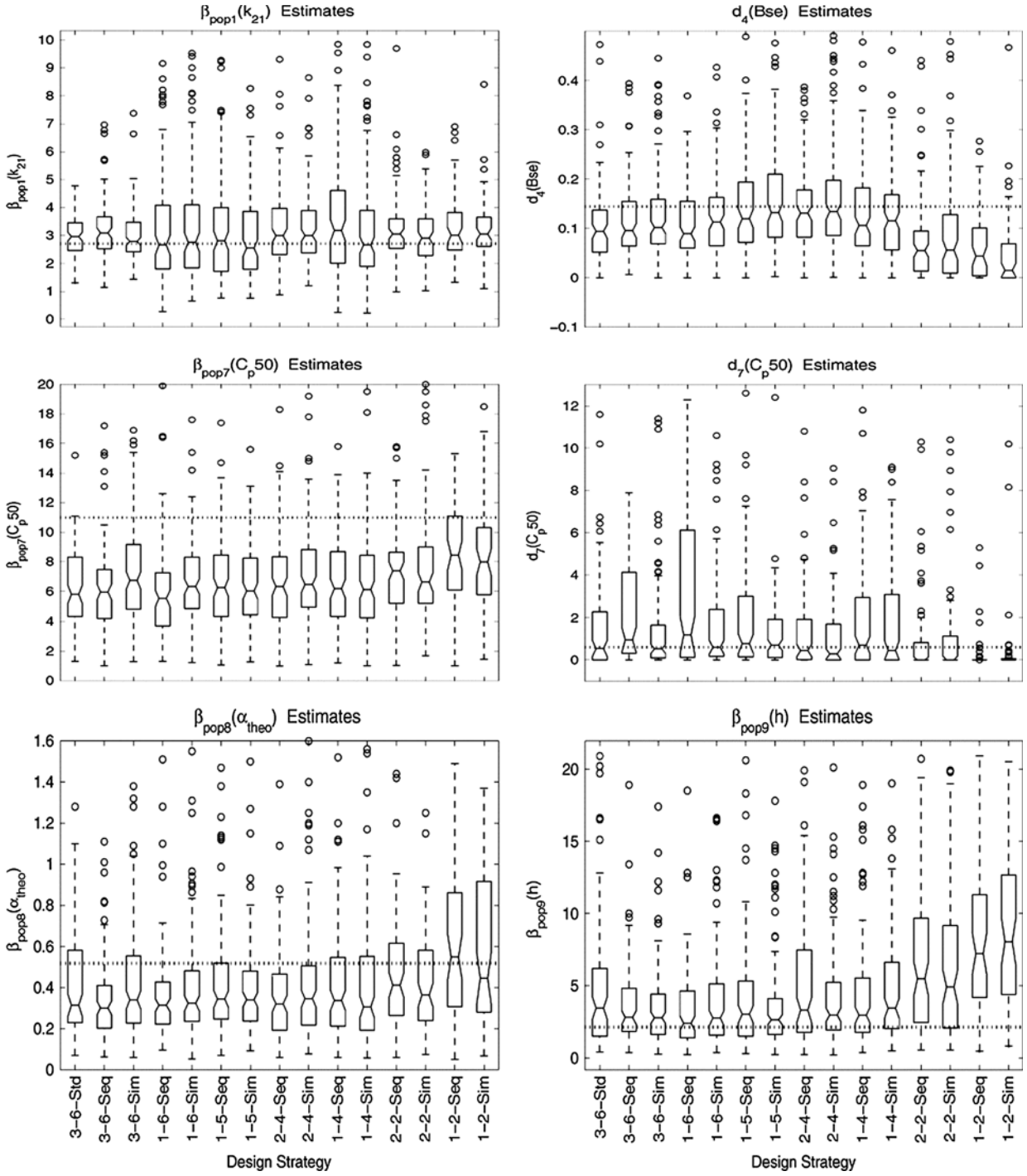

Figure 24. Box plots of parameter estimates for Model 4 using the design strategies outlined in Table 4. The dotted horizontal line is the true parameter value used in the simulations.

of this article has pointed out that a good test model might be a target-mediated drug disposition model such as in Mager and Jusko,[38] although our software is not capable of handling such a complex model at present. Work is ongoing in this area.

Finally, we would like to point out that there are experimental procedures in which SEQ designs could not be used and SIM designs would have to be employed. For example, in PK-PD experiments in which both the PK and PD sampling times must be taken simultaneously, SEQ designs would be impractical. First would be computing the optimal sampling times of the PK experiment. Then, because the PK and PD sampling times must be identical, the PD sampling times would be fixed to the optimal PK times. Thus, the PD sampling times would be computed without any information about the PD model. In contrast, SIM optimal design of the same experiment would allow for both PK and PD

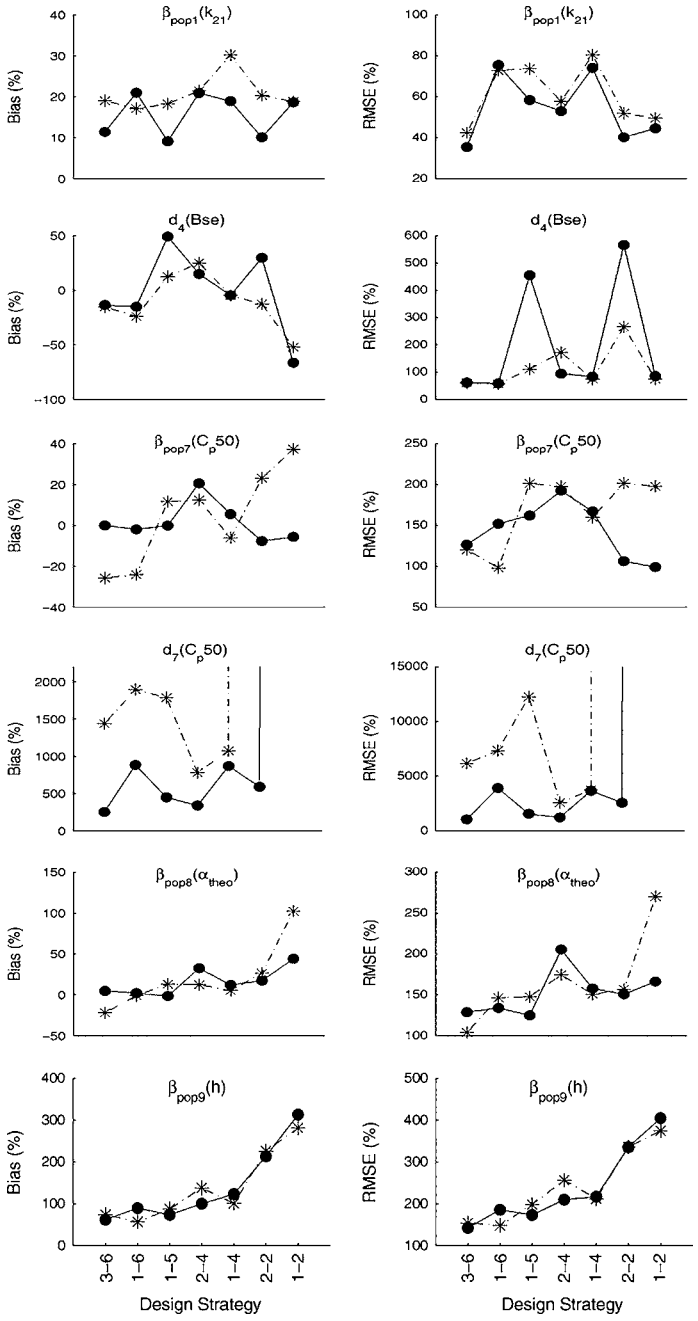

Figure 25. The percentage bias and RMSE for parameters in Model 4. Design methods are outlined in Table 4. (*)- SEQ population optimal designs, (•)- SIM population optimal designs.

information to dictate the placement of the optimal sampling times.

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REFERENCES

1. Breimer DD, Danhof M. Relevance of the application of pharmacokinetic-pharmacodynamic modelling concepts in drug development. The "wooden shoe" paradigm. *Clin Pharmacokinet*. 1997;32:259-267.

2. Levy G. The case for preclinical pharmacodynamics. In: Yacobi A, Skelly JP, Shah VP, Benet LZ, eds. *Integration of Pharmacokinetics, Pharmacodynamics and Toxicokinetics in Rational Drug Development.* New York, NY: Plenum Press; 1993:7-13.

3. Gabrielsson JH, Luthman J, van der Graaf PH. Utility of kinetic-dynamic reasoning in decision making in drug candidate selection. In: Danhof M, Karlsson M, Powel RJ, eds. *Measurement and Kinetics of In Vivo Drug Effects. Advances in Simultaneous Pharmacokinetic/ Pharmacodynamic Modelling. Vol 1.* The Netherlands: Nordwijkerhout; 2002:161-165.

4. US Food and Drug Administration. FDA Modernization Act of 1997. Food and Drug Administration Web site. Available at: www.fda.gov. Accessed October 2003.

5. US Food and Drug Administration. Providing clinical evidence of effectiveness for human drugs and biological products. Food and Drug Administration Web site. Available at: www.fda.gov. Accessed October 2003.

6. D'Argenio DZ. Optimal sampling times for pharmacokinetic experiments. *J Pharmacokinet Biopharm*. 1981;9:739-756.

7. US Congress. *Pharmaceutical R&D: Costs, Risks and Rewards.* Washington, DC: US Government Printing Office; 1993:OTA-H-522.

8. Kaitin KI. *Outlook 2002.* Boston, MA: Tufts Center for the Study of Drug Development, Tufts University; 2002.

9. al-Banna MK, Kelman AW, Whiting B. Experimental design and efficient parameter estimation in population pharmacokinetics. *J Pharmacokinet Biopharm*. 1990;18:347-360.

10. Retout S, Mentre F, Bruno R. Fisher information matrix for non-linear mixed-effects models: evaluation and application for optimal design of enoxaparin population pharmacokinetics. *Stat Med*. 2002;21:2623-2639.

11. Atkinson AC, Donev AN. *Optimum Experimental Designs.* Oxford, UK: Clarendon Press; 1992.

12. Tod M, Padoin C, Louchahi K, Moreau-Tod B, Petitjean O, Perret G. Application of optimal sampling theory to the determination of metacycline pharmacokinetic parameters: effect of model misspecification. *J Pharmacokinet Biopharm*. 1994;22:129-146.

13. Landaw EM. Robust sampling designs for compartmental models under large prior Eigenvalue uncertainties. In: Eisenfeld J, DeLisi C, eds. *Mathematics and Computers in Biomedical Applications.* North-Holland, The Netherlands: Elsevier Science Publishers BV; 1985:181-187.

14. Duffull SB, Mentre F, Aarons L. Optimal design of a population pharmacodynamic experiment for ivabradine. *Pharm Res*. 2001;18:83-89.

15. Mentre F, Dubruc C, Thenot JP. Population pharmacokinetic analysis and optimization of the experimental design for mizolastine solution in children. *J Pharmacokinet Pharmacodyn*. 2001;28:299-319.

16. Mentre F, Mallet A, Baccar D. Optimal design in random-effects regression models. *Biometrika*. 1997;84:429-442.

17. Retout S, Duffull S, Mentre F. Development and implementation of the population Fisher information matrix for the evaluation of population pharmacokinetic designs. *Comput Methods Programs Biomed*. 2001;65:141-151.

18. Merle Y, Tod M. Impact of pharmacokinetic-pharmacodynamic model linearization on the accuracy of population information matrix and optimal design. *J Pharmacokinet Pharmacodyn*. 2001;28:363-388.

19. Zhang L, Beal SL, Sheiner LB. Simultaneous vs sequential analysis for population PK/PD data I: best-case performance. *J Pharmacokinet Pharmacodyn*. 2003;30:387-404.

20. Danhof M, Karlsson M, Powell RJ, eds. Advances in Simultaneous Pharmacokinetic/Pharmacodynamic Modelling. Part 1 and 2. 4th International Symposium on Measurement and Kinetics of In Vivo Drug Effects; April 24-27; Nordwijkerhout, The Netherlands. Leiden, The Netherlands: Leiden University; 2002. 1-200.

21. Davidian M, Giltinan DM. *Nonlinear Models for Repeated Measurement Data.* New York, NY: Chapman & Hall/CRC; 1995:241.

22. Fedorov VV, Hackl P. *Model Oriented Design of Experiments.* New York, NY: Springer-Verlag; 1997.

23. Vonesh EF, Chinchilli VM. *Linear and Nonlinear Models for the Analysis of Repeated Measurements.* New York, NY: Marcel Dekker Inc; 1997.

24. Hooker AC, Foracchia M, Dodds MG, Vicini P. An evaluation of population D-optimal designs via pharmacokinetic simulations. *Ann Biomed Eng*. 2003;31:98-111.

25. Foracchia M, Hooker A, Vicini P, Ruggeri A. POPED, a software for optimal experiment design in population kinetics. *Comput Methods Programs Biomed*. 2004;74:29-46.

26. Larsen RJ, Marx ML. *An Introduction to Mathematical Statistics and Its Applications.* Upper Saddle River, NJ: Prentice-Hall; 1986: 248.

27. Solkner J. Choice of optimality criteria for the design of crossbreeding experiments. *J Anim Sci*. 1993;71:2867-2873.

28. Retout S, Mentre F. Further developments of the Fisher information matrix in nonlinear mixed effects models with evaluation in population pharmacokinetics. *J Biopharm Stat*. 2003;13:209-227.

29. Sheiner L, Wakefield J. Population modelling in drug development. *Stat Methods Med Res*. 1999;8:183-193.

30. Sheiner LB, Stanski DR, Vozeh S, Miller RD, Ham J. Simultaneous modeling of pharmacokinetics and pharmacodynamics: application to d-tubocurarine. *Clin Pharmacol Ther*. 1979;25:358-371.

31. Draper NR, Hunter WG. Design of experiments for parameter estimation in multiresponse situations. *Biometrika*. 1966;53:525-533.

32. Bennett JE, Wakefield JC. A comparison of a Bayesian population method with two methods as implemented in commercially available software. *J Pharmacokinet Biopharm*. 1996;24:403-432.

33. Hashimoto Y, Sheiner LB. Designs for population pharmacodynamics: value of pharmacokinetic data and population analysis. *J Pharmacokinet Biopharm*. 1991;19:333-353.

34. Colburn WA. Simultaneous pharmacokinetic and pharmacodynamic modeling. *J Pharmacokinet Biopharm*. 1981;9:367-388.

35. Mandema JW, Stanski DR. Population pharmacodynamic model for ketorolac analgesia. *Clin Pharmacol Ther*. 1996;60:619-635.

36. Beal S, Sheiner L. *NONMEM User's Guide.* San Francisco, CA: University of California; 1992.

37. Holford N, Hashimoto Y, Sheiner LB. Time and theophylline concentration help explain the recovery of peak flow following acute airways obstruction. Population analysis of a randomised concentration controlled trial. *Clin Pharmacokinet*. 1993;25:506-515.

38. Mager DE, Jusko WJ. Receptor-mediated pharmacokinetic/pharmacodynamic model of interferon-beta 1a in humans. *Pharm Res*. 2002;19:1537-1543.